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MicroRNAs and Regeneration in the Animal Models of CNS Disorders

Tamara Roitbak

Department of Neurosurgery, University of New Mexico Health Sciences Center Albuquerque, NM, USA

Abstract

microRNAs (miRNAs) are recently identified small RNA molecules that regulate gene expression and significantly influence the essential cellular processes associated with CNS repair after trauma and neuropathological conditions including stroke and neurodegenerative disorders.

A number of specific miRNAs are implicated in regulating the development and propagation of CNS injury, as well as its subsequent regeneration. The review focuses on the functions of the miRNAs and their role in brain recovery following CNS damage. The article introduces a brief description of miRNA biogenesis and mechanisms of miRNA-induced gene suppression, followed by an overview of miRNAs involved in the processes associated with CNS repair, including neuroprotection, neuronal plasticity and axonal regeneration, vascular reorganization, neuroinflammation, and endogenous stem cell activation. Specific emphasis is placed on the role of multifunctional miRNA miR-155, as it appears to be involved in multiple neurorestorative processes during different CNS pathologies. In association with our own studies on miR-155, I introduce a new and unexplored approach to cerebral regeneration: regulation of brain tissue repair through a direct modulation of specific miRNA activity. The review concludes with discussion on the challenges and the future potential of miRNA-based therapeutic approaches to CNS repair.

Keywords

microRNA; miR-155; neurorestoration; post-stroke inflammation; cerebral blood flow; functional recovery

Introduction

CNS regeneration after injury is extremely limited, and spontaneous functional recovery is primarily depended upon the intrinsic mechanisms involving neuroprotection, neurogenesis, structural remodeling of spared axons and dendrites, and consolidation of compensatory neuronal circuits within the damaged tissue. These mechanisms involve significant changes in gene and protein expression and activation of complex molecular pathways recruited by

Tamara Roitbak, PhD, Department of Neurosurgery, University of New Mexico Health Sciences Center, 1101 Yale Blvd, Albuquerque, NM 87106-3834, Phone: 505-272-3202, troitbak@salud.unm.edu.

Declaration of Conflicting Interests

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CNS for survival. Among the actively involved molecules recently identified are short RNAs called MicroRNAs (miRNAs). miRNAs, constituting a substantial class of small non-coding RNAs, are characterized by short length (~22 nucleotides) and an extensive potential to suppress protein-coding genes in eukaryotes [1–3]. The discovery of miRNAs, in 1993, introduced a new role of short non-coding RNAs as regulatory molecules and considerably redefined the understanding of post-transcriptional gene regulation [4,5]. After more than 20 years of the extensive investigation, it is now postulated that miRNAs, assembled in the regulatory protein complexes, recognize and bind the complementary sequences of the messenger RNA (mRNA) and alter protein translation and synthesis, as well trigger mRNA destabilization and degradation. Most mammalian genes and more than 60% of human protein-coding genes are believed to be controlled by miRNAs [6]. New animal and plant microRNAs have been identified, and a stunning number and variety of these molecules demonstrate their widespread, prevalent, and important regulatory role. Recently, in addition to 1,900 of the previously known sequences, 3,707 novel mature miRNAs have been identified in 13 different human tissue types [7]. A detailed atlas of miRNA distribution in different human tissues presented the expression profiles of at least 1,300 widely distributed and tissue-specific human miRNAs [8].

microRNA Biogenesis

While initially discovered in the intergenic regions, miRNAs are also derived from intronic or exonic gene sequences. The microRNAs are transcribed in the nucleus, and their nuclear processing is regulated by RNAse III Drosha and its co-factor DGCR8/Pasha. The miRNA precursor is exported into the cytoplasm by Exportin 5, while further modification/maturation is mediated by an endoribonuclease Dicer. A small RNA duplex generated by Dicer associates with the Argonaut family proteins (AGO) which form a so-called RNA-induced silencing complex (RISC or miRISC) [9,10,2]. The unwinding of the AGO-loaded duplex and the generation of single-stranded mature miRNA are now believed to occur concomitantly with the RISC effector complex assembly [11,12]. The mechanism of RISC assembly and its exact composition are still being investigated. RISC is believed to be first assembled by AGO proteins, and to contain miRNA-loaded AGO bound to a glycine-tryptophan repeat-containing protein GW182. During the mRNA silencing, miRNA serves as a guide to target a complimentary mRNA, while miRNA-guided RISC effector protein complex mediates translational repression and/or mRNA degradation (Figure 1). The miRNA-mRNA targeting is governed by base pairing and occurs predominantly at the 3’ untranslated region (3’ UTR) of the target mRNA. A miRNA “seed region” (domain between the nucleotides 2 −7 at the 5′ end) is required for miRNA-mRNA interaction [1,13].

While the majority of miRNAs are generated via canonical pathway, several alternative biogenesis mechanisms are identified. Some unconventional miRNAs can be produced via non-canonical pathways through the nuclear microprocessing by Drosha or cytoplasmic processing by Dicer [14–16]. While the existence of non-canonical pathways exposes the complexity of miRNA biogenesis, the majority of functional miRNAs are generated via the conventional pathway. miRNA biogenesis and miRNA/RISC-induced silencing of the target mRNA is tightly regulated both on transcriptional and post-transcriptional levels. Among the

regulators of miRNA functions are transcription factors such as MYC, p53, ZEB1 and ZEB2; epigenetic factors DNMT1 and DNMT2; RNA-binding proteins; SR proteins; heterogeneous nuclear ribonucleoproteins (hnRNPs); and other factors involved in RNA splicing [17].

miRNA biogenesis is described in detail in a number of reviews [1,9,18,13]. At present, miRNAs are regarded as “master regulators” of gene expression, and “grand managers” of numerous cellular processes, including cell growth, differentiation, maturation, proliferation, migration, interaction with other cells and extracellular components, metabolism, and apoptosis. Therefore, an increasing number of miRNAs are associated with different diseases and pathological conditions [19,1,20].

miRNAs and CNS damage

miRNAs have been found to play an important role during CNS development and they are abundantly expressed in adult human and rodent brain[21–23,7] and spinal cord [24,8]. CNS damage is accompanied by a significant dysregulation in miRNA expression profiles in the affected tissue, peripheral blood, and cerebrospinal fluid. Many research findings detected significant changes in microRNA profiles associated with TBI [25–28], stroke [29,30], epilepsy [31,32], Parkinson’s disease [33,34], Alzheimer’s disease [35,36], and spinal cord injury (SCI) [24,37]. These changes reflect concomitantly occurring injury and self-repair processes, which complicates the interpretation of the obtained data. Therefore, the most important and complicated task for understanding of the function of a specific miRNA is to distinguish whether these various and multiple changes in miRNA expression are harmful or beneficial for the regeneration and repair processes.

Recent findings have identified miRNAs’ novel role as the mediators of intracellular communication. Apart from direct intercellular interactions, crosstalk between neurons, astrocytes, microglia and endothelial cells involves indirect intercellular communication via small extracellular vesicles (EV) secreted by a cell and internalized by its neighboring cells. While various miRNAs can freely circulate in blood and cerebrospinal fluid, a large portion of them is transported as cargo within different types of lipid vesicles [38–40]. Along with proteins, lipids, and different RNA species, miRNAs represent a substantial component of the EV cargo molecules. Among the diverse secreted vesicle population are exosomes, small (30–200 nm) lipid bilayer enclosed vesicles, which recently have been implicated as the major mediators of intercellular microRNA delivery. Secretion of exosomes and their miRNA composition is significantly altered during CNS damage and repair processes [41,42].

miRNA functional analysis is performed to identify genes and processes regulated by specific miRNAs. These studies are based on gain- and loss-of-function experiments utilizing the inhibition or overexpression of miRNAs with specific synthetic inhibitor (antagomirs) or mimic (agomirs) oligonucleotides. While most of the miRNA research is based on *in vitro* experiments, systemic or local administration of the miRNA inhibitors and mimics are utilized to explore the miRNA function in various experimental animal models. In this review, we will focus on the microRNAs, which, based on the functional studies, are

thought to have a profound positive or negative effect on regeneration in the animal models of CNS injury.

The processes and events accompanying CNS regeneration

The subacute phase of CNS injury is accompanied by the active spontaneous recovery process, triggering neuronal plasticity, axonal regeneration, post-injury angiogenesis and vasculogenesis, and neuroinflammation as an integral part of both damage and recovery processes. In addition, CNS damage results in a neurogenic response and a massive migration of neural progenitors into the lesion area, which may substantially contribute to recovery and repair processes [43,44]. All these events are associated with significant changes in gene and protein expression, and are thus broadly regulated by microRNAs. Some excellent reviews describe the involvement of miRNAs in acute and chronic CNS injury and neurodegenerative disorders, accompanied by neuronal and axonal injury, cell apoptosis, vascular damage, aberrant gliosis, and demyelination [45–47]. This review will focus mostly on regeneration, and will describe the miRNAs, which were experimentally proven to have a significant impact on each of the different components of recovery in the animal models of CNS injury.

Neuroprotection

Various microRNAs have been identified as critical regulators of cell survival following CNS injury. They control the levels of various target genes and signaling proteins, which are important for CNS tissue preservation and recovery. These microRNAs control signaling cascades involved in CNS cell survival and apoptosis; among them are components of hypoxia inducible factor −1α (HIF-1 α), mitogen activated protein (MAP) kinase, mammalian target of rapamycin (mTOR), transforming growth factor (TGF-β), Wnt, Notch, and p53 signaling pathways. Recently, the excellent reviews summarized the list of microRNAs, which are up- or down-regulated during the repair process and exerting either protective or damaging effects [48–50]. Based on the recent findings, Table 1 demonstrates some of the regulatory microRNAs and the associated experimentally verified direct target proteins underlying miRNA-based neuroprotection in animal models of CNS injury.

Neuronal plasticity and axonal regeneration

Neuronal plasticity, an intrinsic mechanism by which the CNS responds to the environment, is considerably activated after the injury and is directed toward post-damage survival. In both the brain and spinal cord, a reparative process based on neuronal plasticity includes the repair of damaged neuronal connections, and consists of different stages, such as clearance of debris, axonal sprouting, and formation of new functional synapses [72,73]. These events mainly take place in the peri-infarct or peri-impact area, however more distal (to the injury) portions of the CNS also undergo neuroanatomical changes, and thus contribute to the adaptation and compensation of impaired function. Axonal regeneration depends on the activity of different intrinsic and extrinsic factors that either inhibit or promote neuronal plasticity. The regeneration process is significantly impeded by multiple processes accompanying a sub-acute phase of injury, including generation of free radicals, ongoing demyelination, neuronal death, delayed cell death, activation of astrocytes and

oligodendrocytes, formation of the barrier for the axonal sprouting, and a direct inhibition of neurite outgrowth [72,74]. Among the molecules, which inhibit post-injury plasticity are chondroitin sulphate proteoglycans and NogoA, while Inosine, Activin and other members of TGF-β family exert a neuroprotective effect and support neurite growth and axonal regeneration [72,75]. Many of these significant molecular pathways are believed to be also regulated by microRNAs [76–78]. *In vivo* experimental manipulation of the expression levels of several miRNAs has been proven beneficial for neurite outgrowth and axonal regeneration in the animal models of CNS injury. Among these microRNAs and their experimentally verified targets (shown in parenthesis), are: MicroRNA-431(Kremen1) [79]; miR-210 (EFNA3) [80]; miR-182 (BCAT2) [81]; miR-34a (synaptotagmin-1 SYT-1 and CTX1A) [82]; miR-127 (mitoNEET) [83]; miR-21 (PDCD4) [84]; and miR-320 (ARPP-1) [85].

Vascular reorganization

Significant vascular disfunction is associated with CNS trauma, stroke, and neurodegenerative disorders, including mild cognitive impairment and dementia, Alzheimer's disease, arteriolosclerosis and cerebral amyloid angiopathy (small vessel disease), Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and chronic traumatic encephalopathy [86,87]. Primary and secondary CNS injuries are associated with significant endothelial cell damage, which leads to destruction of microvasculature and development of hemorrhagic and ischemic states. Vascular injury and disfunction are followed by significant impairment and loss of the brain and spinal cord tissue [88,89]. Spontaneous regeneration processes involves post-injury angiogenesis and vasculogenesis [90,91]. The number of specific miRNAs is implicated in regulating endothelial morphogenesis and vascularization [92,93]. Vascular morphogenesis is a complex process that involves an intricate interplay between multiple cell signaling pathways. Formation of new capillaries includes endothelial cell morphogenesis, and subsequent maturation of intercellular junctions and the surrounding basement membrane. These stages are influenced by the number of signaling proteins, including VEGF, Notch, and TGF-β [94,95]. There are a number of miRNAs that are linked to the endothelial cell morphogenesis [96] in general, and particularly, in post-injury vascular remodeling [97,98]. In addition to the vascular reorganization, microRNAs regulate endothelial tight junctions, and thus, significantly influence the integrity and permeability of the blood brain barrier (BBB) and the blood-spinal cord barrier (BSCB). A significant number of microRNAs wave been implicated in regulating the endothelial barrier function through alteration of the expression levels and functions of the endothelial tight junction and the adherens junction proteins, including claudins, occludin, zonula occludens protein family (ZO-1,−2 and-3), VE-cadherin, and their regulatory signaling molecules [99–102]. Several regulatory microRNAs and their experimentally verified targets have been identified as the mediators of different molecular pathways involved in endothelial integrity and vascular remodeling in the animal models of CNS injury. Among them are miR-320a (AQP1) [102]; miR-363 (Timp-1 and THBS3) [103]; miR-150 (VEGF) [104]; and miR-155 (Annexin-2, claudin-1, DOCK-1, Rheb) [105,106].

Neuroinflammation

Post-injury inflammatory response represents an integral part of the injury, defense response, and recovery after CNS trauma, hypoxia, infection, and neurodegeneration. Neuroinflammation is associated with the elevation of cytokines; recruitment of neutrophils, lymphocytes, and monocytes; and activation of resident microglia, astrocytes, and endothelial cells. The cellular inflammatory response leads to the additional release of cytokines/chemokines and other pro-inflammatory factors [107,108]. While it is known that lower levels of pro-inflammatory cytokines and higher expression of anti-inflammatory cytokines are associated with a better clinical outcome, it is also accepted that inflammation-associated events play an active role in tissue remodeling and recovery. Among different factors triggered by the “injury” signals from the damaged CNS tissue are cytokines such as interleukins −1, −6, −4, −10 (IL-1α and IL-1β, IL-6, IL-4, IL-10) released within minutes after the insult, tumor necrosis factor-α (TNFα), interferon-γ (IFNγ), nitric oxide (NO), and cyclooxygenase-2 (COX-2) [109–111]. All these factors are context-dependent, and, at different times during the inflammation, exert either pro- or anti-inflammatory functions. Cytokine signaling is mediated via essential signaling pathways including JAK/STAT pathway, and negatively regulated by a number of molecules, such as SHIP-1, and SOCS family proteins. microRNAs are now known to be actively involved in every aspect of neuroinflammation, including the dynamic changes in cellular response and cytokine release/signaling, monocyte recruitment and infiltration, the interaction between different types of resident and infiltrated cells, and the de-activation and resolution of neuroinflammation. Based on these multiple regulatory functions, it is evident that miRNAs have an essential influence on both innate and adaptive immune responses. Increasing evidence supports the involvement of miRNAs as key regulators of neuroinflammation associated with various CNS pathologies [112–114]. Table 2 summarizes the list of regulatory microRNAs and their targets, which, after the interventional changes in their expression (inhibition or overexpression), modulate neuroinflammation and recovery in the animal models of CNS injury.

Endogenous stem cell activation

In the adult mammalian brain, neural stem/progenitor cells (NSPCs) are primarily restricted to the subventricular zone of the lateral ventricles and subgranular zone of the dentate gyrus, and, in low numbers, in septum, striatum, and cortex. NSPCs have been identified in the spinal cord (the ependymal cell layer lining the central canal), optic nerve, and retina, where neurogenesis persists throughout adulthood [121–123]. The external signals and intracellular mechanisms that control NSPC generation, function and behavior following injury have been studied intensely, and various aspect of neuronal replacement and cell-based therapy have been introduced. In this review, we focus on the contribution of the endogenous neural stem cells to repair mechanisms, and the possible regulation of this process by microRNAs.

Neurogenesis—It is well established that oxygen is an important signal in all major aspects of stem cell biology. *In vivo* studies utilizing experimental models of ischemia showed that NSPCs strongly respond to hypoxia by massive proliferation and migration towards the stroke-induced brain lesion [43] indicating the importance of the NSPCs in the adaptation and possible recovery following acute brain damage or prolonged pathological

conditions. Functional recovery from TBI is accompanied by active neurogenesis primarily in the hippocampal dentate gyrus [124–126]. In the spinal cord, neurogenesis occurs in response to specific kinds of spinal injury, including dorsal root lesion, compression, contusion, or dorsal funiculus incision [127–130].

Activation, proliferation, and differentiation of NPSCs in specific regions of the CNS are accompanied by significant changes in gene and protein profiles, which together lead to the upregulation of pro-neurogenic cell signaling cascades. Recent findings demonstrate that miRNAs specifically regulate neurogenesis, including the proliferation, migration, cell fate determination, and differentiation of various stem cell populations during CNS development and injury [131–134]. Most of these studies have been executed using neural stem/progenitor cells *in vitro*. Several studies utilizing the *in vivo* inhibition or overexpression approaches, identified the miRNAs and their direct targets that are actively involved in the endogenous stem cell activation in the animal models of CNS injury. It has been demonstrated that miR-7 overexpression resulting in suppression of its direct target NLRP3, supports SVZ neurogenesis in the animal model of Parkinson's disease [135]. In the animal models of stroke, overexpression of miR-124a supports neurogenesis by directly targeting JAG1 protein [136], and miR-17–92 cluster mediates neural progenitor cell proliferation via its target protein PTEN [137].

Oligodendrogenesis—A small portion of SVZ neural progenitors produces oligodendrocyte progenitor cells (OPCs), which migrate into the white matter and cortex [138]. Loss of oligodendrocytes and demyelination associated with CNS damage are accompanied by active oligodendrogenesis, spontaneous remyelination, and myelination of new sprouting axons [139–141]. These processes are associated with the activation of parenchymal and SVZ-derived oligodendrocyte progenitor cells, and their migration toward the lesion [142–145]. It has been demonstrated that following CNS damage induced by stroke, OPCs migrate out of the SVZ and differentiate into myelin forming oligodendrocytes [146,140]. The number of OPCs significantly increases after TBI and spinal cord injury, which could contribute to the repair process by improving white matter function [147–150]. miRNAs have been identified as key regulators of oligodendrocyte functions, myelination, and OPCs generation and differentiation [151,140,152]. Functional *in vivo* studies have identified that increased expression of miR-146a promotes stroke-induced oligodendrogenesis [153], while overexpression of miR-219 after LPC-induced demyelination supports OPC maturation and regeneration processes in mice [154]. Transgenic mice with overexpressed miR-23a in oligodendrocytes demonstrated enhanced oligodendrocyte differentiation and myelination of CNS axons [155].

Multifunctional miRNA miR-155

Several miRNAs have been directly associated with different types of CNS pathologies. Among them is miR-155, a multifunctional and broadly conserved miRNA implicated in regulating various physiological and pathological processes. MiR-155 is processed from an exon of a noncoding RNA transcribed from the B-cell Integration Cluster (BIC) located on chromosome 21. BIC shows strong sequence homology among human, mouse, and chicken, implying an evolutionary conserved function [156–158]. miR-155 is specifically expressed

in hematopoietic cells and cells involved in vascular remodeling [159,160]. In the brain tissue, the expression of miR-155 has been detected in the cerebrovascular endothelium, astrocytes, and microglia [158,161,162]. Apart from being regarded as a major pro-tumorigenic and pro-inflammatory miRNA, this miRNA is implicated in regulating hematopoietic lineage differentiation, endothelial and vascular function, and the progression of cardiovascular diseases [156,157,163]. Silencing of this miRNA is accompanied by reduced inflammation and improved regeneration processes [164–166].

Stroke-associated ischemic damage involves blood-brain barrier dysfunction, microvascular injury; post-ischemic inflammation; and, ultimately, the death of neurons, glia, and endothelial cells, which directly contributes to cerebral tissue damage and neuronal death [167,88,168]. miR-155 is involved in the progression of multiple CNS disorders and pathological conditions. Its increased expression is associated with poor prognosis in patients with amyotrophic lateral sclerosis [169], epilepsy [170], multiple sclerosis [171], and brain tumor [172,173]. miR-155 upregulation was detected in the animal model of stroke, while miR-155 inhibition supported post-stroke recovery [63,106]. Cerebral ischemia induces a cascade of biological events involving activation and upregulation of specific genes and cell signaling pathways, which is an essential component of post-stroke recovery. miR-155 and its target genes and proteins might play a significant role in the regeneration after stroke. Among predicted and experimentally identified miR-155 targets, with possible effect on stroke progression and outcome, are Rheb, Rictor, SMAD-5, SOCS-1, SHIP-1, and C/EBP-β [174,106,175,176]. In addition, it has been demonstrated that major TJ protein claudin-1 is a direct target of human miR-155 [105,177]. As the essential components of the mTOR, TGF-β/BMP, NO, PI3K/Akt, and JAK/STAT signaling pathways, these molecules broadly influence vascular function, neuroinflammation, and brain tissue remodeling.

Effect of systemic miR-155 inhibition after the experimental cerebral ischemia

Effect on cerebral vasculature—The *in vitro* studies identified miR-155 as a potential regulator of the endothelial morphogenesis: specific miR-155 antisense inhibitors supported capillary-like tube formation by the mouse brain endothelial cells [174]. Further experiments revealed that miR-155 inhibition improved HBMEC monolayer integrity and barrier function after oxygen glucose deprivation (OGD). In addition, miR-155 inhibition significantly increased the levels of major endothelial tight junction (TJ) proteins claudin-1 and ZO-1. Based on the detected association between ZO-1 and claudin-1 and their stabilization at the endothelial membrane, it was concluded that miR-155 inhibition strengthens the endothelial TJs after the OGD via stabilization of its direct target protein claudin-1.

Intravenous injections of a specific anti-miR-155 inhibitor, initiated at 48 hours after mouse distal middle cerebral artery occlusion (dMCAO), lead to a significant improvement of cerebrovascular functions, which reflected a significant enhancement of blood flow in the peri-infarct area, improvement of vascular integrity, and preservation of the capillary TJs.

Effect on brain damage and post-stroke neuroinflammation—An assessment of the brain tissue damage using MRI and electron microscopy (EM) demonstrated that at three

weeks after stroke there was a significant (34%) reduction of the infarct size and a significant decrease in neuronal damage in miR-155 inhibitor-injected animals, as compared to the control group. miR-155 inhibition after dMCAO significantly altered the time course and the expression levels of the major cytokines (including IL-10, IL-4, IL-6, MIP-1α, IL-5, and IL-17) as well as considerably modified the microglia/macrophage phenotype in the peri-infarct area of stroke. Electron microscopy-based quantification detected a decreased number of phagocytically active peri-vascular microglia/macrophages in these animals [175].

Effect on the overall post-stroke recovery—Assessment of sensorimotor deficits (bilateral asymmetry/adhesive removal test) and gait/locomotion recovery (CatWalk system), as well as the weight-gain evaluation, indicated that the inhibitor-injected animals regained their sensorimotor deficits and recovered faster than controls [106]. Experiments utilizing miR-155 inhibition in the rat model of cerebral ischemia also demonstrated the efficacy of anti-miR-155 treatment in rats [63].

Molecular mechanisms of miR-155 inhibition-induced support of post-stroke recovery—Based on all of the findings described above, it is possible to conclude that miR-155 inhibition has a beneficial effect on the regeneration after stroke. Systemic inhibition of miR-155 following the experimental cerebral ischemia supports cerebral microvasculature and improves cerebral blood supply to the peri-infarct area of stroke. These improvements are achieved via direct preservation of TJ integrity and suppression of early stage post-stroke inflammation. This recovery mechanism is facilitated by: 1) the initial preservation of vascular integrity, which prevents the propagation of the ischemic damage into the peri-infarct area; 2) the activation of IL-10-mediated neuroprotective mechanisms; and 3) transition from harmful phenotype toward the neuroprotective and reparative microglia/macrophage phenotype. All these support mechanisms could be mediated via the activation of miR-155 direct target proteins, including Rheb, SMAD-1, SMAD-2, SMAD-5, Rictor, eNOS, SOCS-1, SHIP-1, and C/EBP-β (Figure 2).

miRNAs as the markers and therapeutic targets for CNS regeneration

The expression profiles of the miRNAs circulating in cerebrospinal fluid and blood reflect the molecular pathophysiology associated with CNS damage, thus making them promising biomarkers in diagnosis and prognosis of CNS trauma, diseases, and pathological conditions. There is an intensive search for the biomarkers of CNS damage focused on miRNA expression changes in blood, CSF, and saliva. The results are however characterized by significant variations, as they critically depend on methodology, timing of sample collection, and the disease form and stage (acute, subacute, chronic, etc.). To avoid these variable factors, the standardized protocols for circulating miRNA are needed for future studies [178]. Among the wide range of identified miRNAs, some are now considered as biomarkers for severity and prognosis for patients with Parkinson’s disease (miR-30b, miR-30c, miR-26a, miR-133b, and miR-126 [179,180]), acute ischemic stroke (let-7b, miR-16, miR-21, miR-106b, miR-320d, and miR-1246 [181]), Alzheimer’s disease (miR-29b-1, miR-29a, and miR-9 [182], spinal cord injury (miR-21, miR-133b, miR-9–3p, miR-219, miR-384–5p, mir-204–5p, mir-519d-3p, mir-20b-5p, and mir-6838–5p,

[183,184]), and TBI (miR-1255b, miR-151–5p, miR-194, miR-195, miR-199a-3p, miR-20a, and miR-27a among others [185]). Please see the complete lists of miRNAs considered potentially to be used as biomarkers of CNS aberrations in previously published reviews [178],[186],[187].

As the changes in miRNA profiles strongly correlate with different CNS pathologies, a number of these small RNAs are considered to be used for targeted therapeutic approaches to enhance the regeneration processes in the future. Several miRNA-based therapies, focusing on targeted inhibition of specific miRNAs, have been recently introduced and supported by the leading RNA-therapeutic companies [188]. While several of these investigations remain in the pre-clinical stage, some of them, involving miR-122 inhibitor miravirsen or miR-34a inhibitor MRX34, have already entered into a phase II clinical trial for hepatitis C, and a phase I clinical study for cancer treatments, respectively. The studies demonstrate a substantial, prolonged, and highly specific decrease in plasma miR-122 levels in patients receiving subcutaneous injections of miravirsen [189]. MRX34 treatment demonstrated an acceptable safety and antitumor activity in patients with solid tumors [190]. Antagomir-based therapeutics have been potentially indicated for various human diseases and pathological conditions, including kidney disease (targeting miR-21), diabetes/obesity (using anti-miR-208), erythrocyte deficiency (anti-miR-451), and myocardial infarction (anti-miR-15) [188]. Despite the intense interest in the innovative miRNA targeting therapies, there are currently no trials related to CNS damage and repair. However, the emerging role of miRNAs as therapeutic agents for treatment of CNS pathologies has been proposed by numerous researchers and summarized in several recent reviews [191,178].

One of the major challenges of miRNA-based therapy is to achieve specific, safe, and efficient modulation of miRNAs. While the oral administration of miRNA inhibitors (or mimics) is inefficient, subcutaneous and intravenous delivery of oligonucleotides is also problematic because of their instability and limited bioavailability. Therefore, lipid-based delivery vehicles, viral vectors, nanoparticle-conjugated oligonucleotides, and biodegradable polymers are utilized for the introduction of synthetic miRNA inhibitors and mimics. Recently developed locked nucleic acid (LNA)-based technology greatly increased the pharmacokinetic properties of the miRNA inhibitors/mimics, improved their resistance to enzymatic degradation, and minimized off-target effects. As a future development, miRNA-based technology is expected to establish more sophisticated delivery systems targeting specific cells in human organisms. One of the novel approaches in miRNA-based therapy involves the exosome-mediated delivery of specific functional miRNAs. It has been proposed that administration of specific miRNA-enriched exosomes could be used as a therapy for stroke, TBI and other CNS pathologies [192–194]. Among the miRNAs involved in the beneficial effect of treatment with mesenchymal stromal cell-derived exosomes, are miR-133b and miR-17–92 cluster [195–197].

Besides the direct inhibition/overexpression of miRNAs using synthetic oligonucleotides or miRNA-enriched exosomes, a different approach could be pursued focusing on certain known drugs with a modulatory effect on certain miRNAs. In addition to the earlier described pharmaceutical compounds [178], several more drugs have demonstrated a strong and prolonged effect on specific miRNA expression in damaged CNS. Among them are:

acetylbritannilactone (suppresses miR-155 expression), which reduces neuroinflammation after ischemia in mice [198]; resolvin D1 (targets miR-146b and miR-219a), which promotes recovery after the focal brain damage in rats [199]; dexmedetomidine (suppresses miR-124, −132, −134, and −155 [200]) and hesperidin (upregulates miR-132 [201]), which reduce neuroinflammation in LPS-treated rat brain; arctigenin (upregulates miR-16 and miR-199a), which provides neuroprotection against mechanical trauma injury in human neural cells [202]; amikacin (inhibits miR-497 maturation), which provides neuroprotection after the *in vitro* ischemia [203]; calycosin (upregulates miR-375) with a protective effect following ischemia/reperfusion in rats [204]; and finally, lithium, which was found to promote miR-124 expression and have a neuroprotective effect in the mouse model of stroke [205]. In addition, a number of natural agents have been found to have a strong modulatory effect on miRNAs. Interestingly, miR-155 is suppressed by turmeric, a polyphenolic compound derived from the dietary spice turmeric, known to have anti-inflammatory and anti-tumorigenic properties [206]. Natural compounds, including resveratrol, genistein, epigallocatechin-3-gallate, indole-3-carbinol, and other agents regulating miRNA expression are discussed in detail in recently published reviews [207,208].

Conclusion

Dysregulated miRNA functions following CNS damage have profound effects on their target genes, which are involved in both the progression of the CNS injury and the subsequent recovery process. Numerous studies have identified a number of miRNAs and their target genes, which are involved in the CNS repair process, promoting neuroprotection, neurogenesis, axon regeneration, neuronal plasticity, angiogenesis, and vasculogenesis. The associated changes in miRNA profiles provide evidence that many of them could be considered as markers for CNS damage and/or repair, and that their modulation could be beneficial for recovery. Thus, miRNAs represent an important class of molecules, which offer an understanding of CNS damage and repair, and represent the ideal biomarkers for diagnosis and prognosis. Most importantly, a targeted modulation of specific miRNA expression has promising potential as a strategy for treatment of CNS injuries. Despite the current challenges, miRNA-based therapy is expected to become an effective and innovative pharmaceutical approach in the future.

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Abbreviations:

NogoA	neurite outgrowth inhibitor
TGF-β	Transforming growth factor beta
VEGF	vascular endothelial growth factor
VE-cadherin	vascular endothelial cadherin
TBI	traumatic brain injury

Rheb	Ras homolog enriched in brain
mTOR	mammalian target of rapamycin
Rictor	Rapamycin-insensitive companion of mammalian target of rapamycin
C/EBP-β	CCAAT/enhancer-binding protein beta
BMP	Bone morphogenetic protein
NO	nitric oxide
JAK	Janus kinase
STAT	signal transducers and activators of transcription
SOCS	suppressor of cytokine signaling
SHIP	Src homology 2 (SH2) domain-containing protein-tyrosine phosphatase
LPS	Lipopolysaccharide

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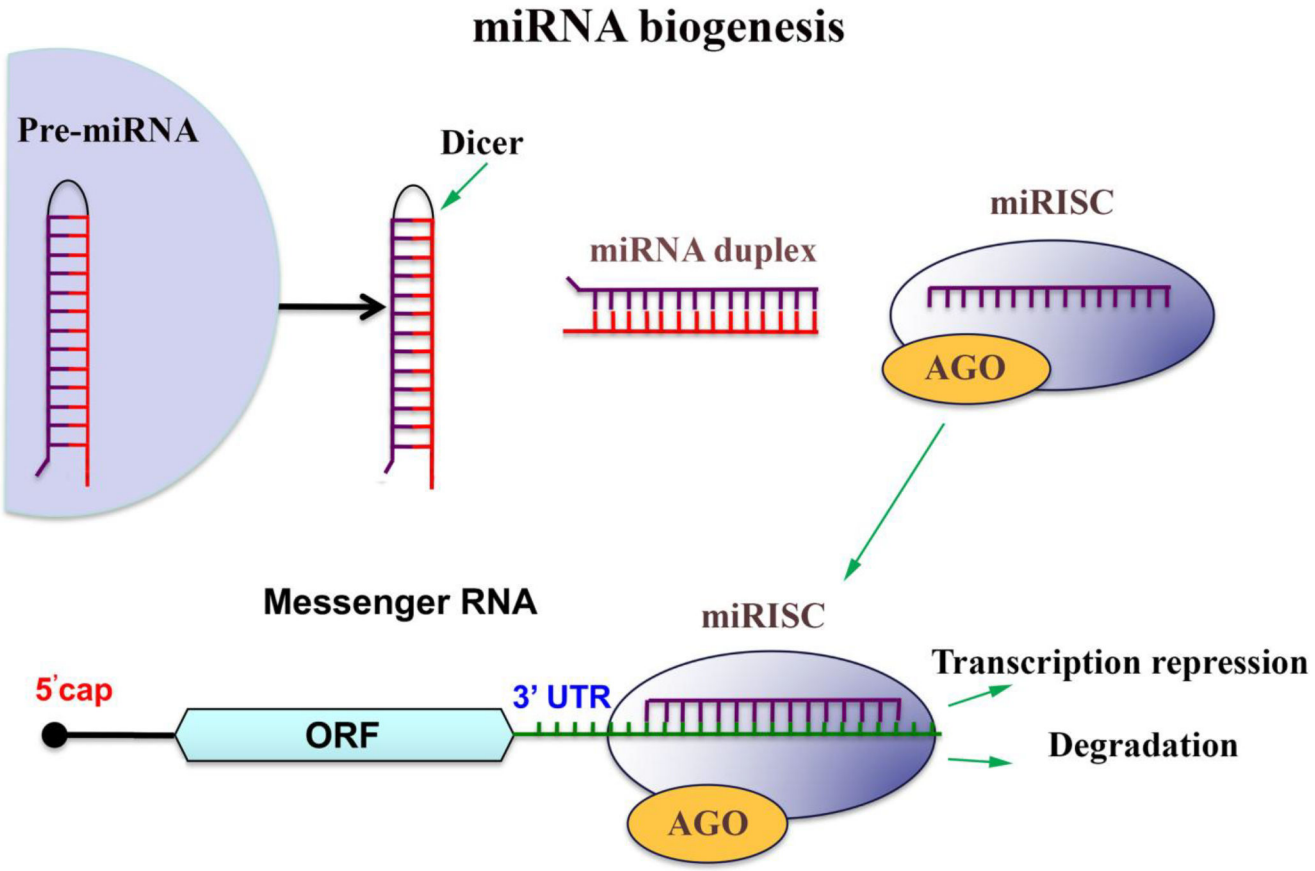

Figure 1: Canonical pathway of miRNA biogenesis.

The microRNAs are transcribed in the nucleus, the miRNA precursor is exported into the cytoplasm, and further modification/maturation is mediated by an endoribonuclease Dicer. A small RNA duplex generated by Dicer associates with the Argonaut family proteins (AGO) which form a so-called RNA-induced silencing complex (miRISC). RISC effector complex assembly involves the unwinding of the AGO-loaded duplex and generation of single-stranded mature miRNA. During the mRNA silencing, miRNA serves as a guide to target a complimentary mRNA, while miRNA-guided RISC effector protein complex mediates translational repression and/or mRNA degradation.

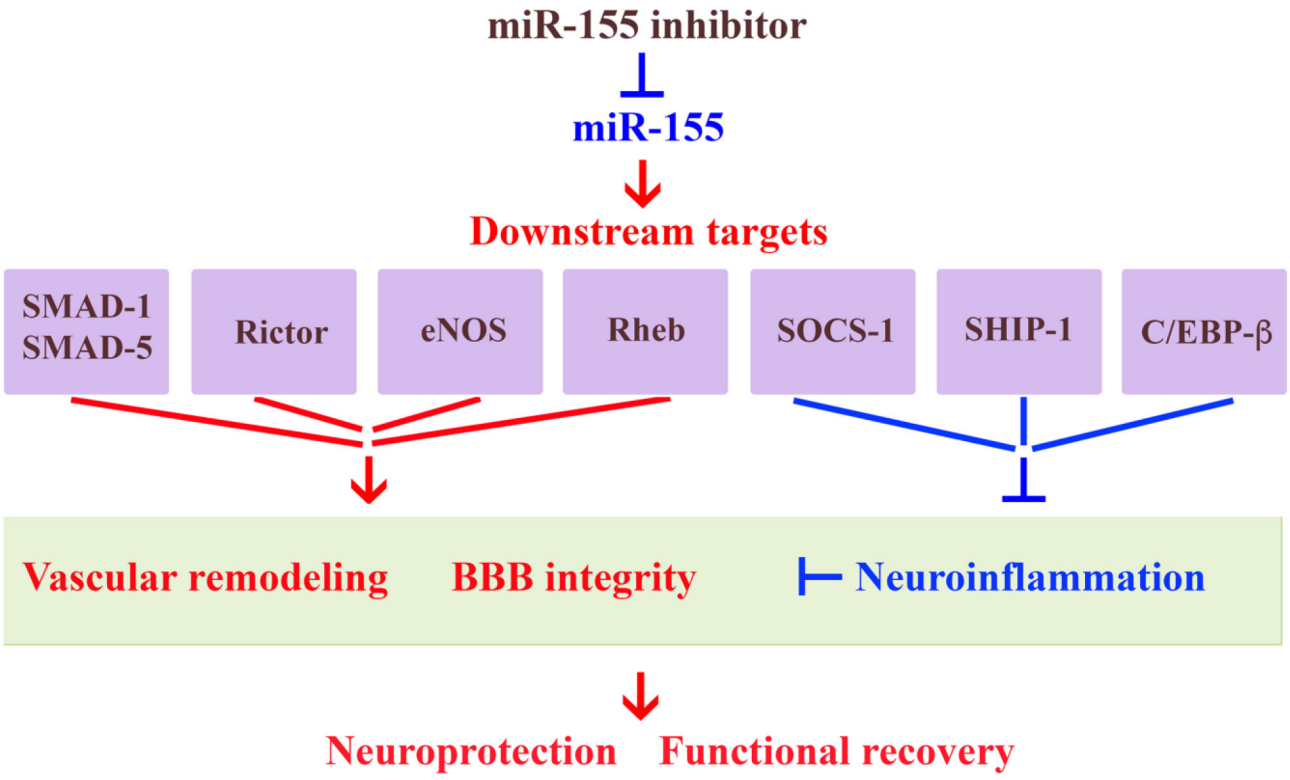

Figure 2: Possible molecular mechanisms mediating functional recovery supported by *in vivo* miR-155 inhibition after stroke.

miR-155 inhibition results in the increased expression of miR-155 target proteins SMAD-1 and SMAD5 (components of BMP signaling pathway), Rictor (mTOR pathway), eNOS (NO pathway), Rheb (activates Akt/ZO-1 pathway), which support microvascular function and strengthen the BBB integrity. Upregulation of other miR-155 targets, such as SOCS-1 and SHIP-1 (which suppress JAK/STAT-mediated cytokine signaling), and C/EBP (which activates anti-inflammatory IL-10), regulate post-stroke neuroinflammation and thus, support vascular integrity and neuronal survival. As a result, miR-155 inhibitor-induced support of BBB integrity leads to the reduction of brain edema, restoration blood flow in the peri-infarct area of stroke, and prevents delayed neuronal death in the peri-infarct area. This results in the reduced brain infarct, neuroprotection and improved functional recovery. Red font/arrow indicate upregulation/activation; blue - downregulation/inhibition.

Table 1:

***In vivo* inhibition or overexpression of specific microRNAs supports neuroprotection in the animal models of CNS injury.**

Table 1 summarizes the list of regulatory microRNAs and their targets, which, after the experimental intervention using miRNA inhibitors and mimics, support neuronal survival and facilitate recovery in the animal models of CNS injury. The process is mediated via the experimentally verified direct target genes/proteins.

miRNA	Animal model of CNS injury	Treatment	Involved direct miRNA targets
miR-210	Stroke	Overexpression	mBDNF/proBDNF [51]
miR-124	Stroke	Overexpression	Bcl-2 and Bcl-xl [52]; Usp14 [53]
miR-216a	Stroke	Overexpression	JAK2 [54]
miR-29b	Stroke	Overexpression	Aquaporin-4 [55]
miR-29c	Stroke	Overexpression	Birc2 [56]
miR-128–3p	Stroke	Overexpression	p38α [57]
miR-93	Stroke	Overexpression	Nrf2 [58]
miR-223	Stroke	Overexpression	GluR2 and NR2B [59]
miR-378	Stroke	Overexpression	Caspase-3 [60]
miR-181	Stroke	Inhibition	BCL2 and XIAP [61]
miR-181b	Stroke	Inhibition	HSPA5 and UCHL1 [62]
miR-155	Stroke	Inhibition	Rheb [63]
miR-30a	Stroke	Inhibition	HSPA5 [64]
miR-27a	TBI	Overexpression	FoxO3a [50]
miR-144	TBI	Inhibition	ADAM-10 [65]
miR-124	Parkinson’s disease	Overexpression	Bim [66]
miR-7	Parkinson’s disease	Overexpression	α-Synuclein [67]
miR-210	CSI	Overexpression	PTP1B and ephrin-A3 [68]
miR-125b	CSI	Overexpression	Sema4D [69]
miR-486	CSI	Inhibition	NeuroD6 [70]
miR-20a	CSI	Inhibition	Ngn1 [71]

Table 2:

***In vivo* inhibition or overexpression of specific microRNAs alters neuroinflammation in the animal models of CNS injury.**

Table 2 summarizes the list of regulatory microRNAs and their targets, which, after the experimental intervention using miRNA inhibitors and mimics, modified the inflammation and supported recovery in the animal models of CNS injury. The process is mediated via the experimentally verified direct target genes/proteins.

miRNA	Animal model of CNS injury	Treatment	Involved direct miRNA targets
miR-200b	TBI	Overexpression	c-Jun [115]
miR-3473b	Stroke	Inhibition	SOCS3 [116]
miR-155	Stroke	Inhibition	SOCS-1, SHIP-1, and C/EBP-β [106]
miR-let-7c	TBI	Overexpression	Caspase-3 [117]
miR-27a	LPS-induced neuroinflammation (animal model of AD, PD, and ALS)	Overexpression	TLR4 and IRAK4 [118]
miR-367	Intracerebral hemorrhage	Overexpression	IRAK4 [119]
miR-21	EAE	Inhibition	SMAD-7 [120]