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REVIEW PAPER

MicroRNA-21 in the Pathogenesis of Traumatic Brain Injury

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Abstract
MicroRNAs (miRNAs), an abundant class of small noncoding RNA molecules, which regulate gene expression by functioning as post-transcriptional regulatory factors, have been identified as key components of traumatic brain injury (TBI) progression. MicroRNA-21 (miR-21) is a recently identified typical miRNA that is involved in the signaling pathways of inflammation, neuronal apoptosis, reactive gliosis, disruption of blood brain barrier, angiogenesis and recovery process induced by physical exercises in TBI. Hence, miR-21 is now considered as a potential therapeutic target of TBI. We review the correlative literature and research progress regarding the roles of miR-21 in TBI in this article.

Keywords MicroRNA · MicroRNA-21 · Traumatic brain injury

Introduction

With the development of society, TBI has been a leading cause of death and disability among adults [1, 2]. Half of all traumatic deaths in the USA are due to brain injury [3]. Survivors are also at risk for lowered life expectancy, face long term physical, cognitive and psychological disorders that greatly diminish quality of life [4]. Despite more and more research on it, there is no effective pharmacologic treatments in TBI [5]. A better understanding of the molecular mechanisms underlying TBI is imperative to develop effective strategies for treatment and monitoring. TBI triggers multiple molecular and cellular changes that underlie its pathophysiology and outcome, including inflammation, neuronal apoptosis, reactive gliosis and disruption of BBB [6–9].

MicroRNAs (miRNAs) are an abundant class of small (approximately 22 nucleotides) noncoding RNA molecules which are highly conserved, regulate gene expression by functioning as a post-transcriptional regulatory factor. They can induce mRNA degradation, translational repression mediated by pairing with partially complementary sites in the 3′UTR of target genes [10]. Over 5000 miRNAs likely exist in humans, and they target 30–80% of protein-coding genes [11–13]. Each miRNA regulates translation of hundreds of distinct mRNAs [14]. So they play a central role in many biological processes, including cell cycle [15], cell metabolism [16], apoptosis [17] and immune responses [18]. It has been recently demonstrated that miRNAs have also been identified as key components of TBI progression [19]. miR-335 and miR-21 were significantly upregulated and are valid biomarkers for the diagnosis of severe TBI [20]. miR-711 up-regulation induces neuronal cell death after traumatic brain injury [21]. Roles of miRNAs in regulating neuroinflammation have also been identified [22].

miR-21 has been reported as an oncogene [23], which expresses ubiquitously in mammal organ systems, such as spleen, heart, kidney, brain [24]. It increases cell proliferation and reduces apoptosisin the pathological process of tumors by regulating cellcycle and apoptosis-related gene [25, 26]. miR-21 is also involved in the pathological process of cerebral infarction and glioblastoma multiforme (GBM). It is upregulated in stroke patients [27] and in the brain of rats subjected to middle cerebral artery occlusion [28]. miR-21 could protect against ischemic neuronal death and promote the nerve cell regeneration by down-regulating PDCD4 (Programmed cell death protein 4) [29] and factor associated suicide ligand (FasL) [30]. So it is now identified as a potential markers of acute cerebral infarction [31]. miR-21 is also identified as a diagnostic and therapeutic biomarker for GBM patients. It is associated with cell division, apoptosis and angiogenesis in progression of GBM. Insulin-like

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growth factor (IGF)-binding protein-3 (IGFBP3) [32], SOX2 [33] and vascular endothelial growth factor (VEGF) [34] are identified as targets of miR-21. In GBM patients, mitotic protein kinase (MPS1) could influence the expression of tumor suppressors via modulating miR-21 [35].

More recently, miR-21 has also been involved in the intricate process of TBI course and may be a potential therapeutic target [36]. In this review, we summarize our current knowledge about the role of miR-21 and its mechanism that is potentially associated with TBI pathogenesis.

miR-21 is Upregulated After TBI

Lei et al. employed microarray to analysis microRNA expression in rat cerebral cortex after TBI, the results showed that miR-21 were more than twofold up-regulated after TBI [37]. Redell et al. also reported the wide spread expression of miR-21 in normal brain of rodents, with a pronounced increase in expression after TBI evident throughout the cortex and hippocampus, peaking by 3 days and returning to near sham levels by 15 days after TBI [38]. In fluid percussion injury rat model, combined miRNA in-situ hybridization (ISH) and immunofluorescence (IF) staining was used to measured the in-situ expression of miR-21 in various cells (neurons, astrocytes and microglias) of the central nervous system (CNS), the result showed that the expression levels of miR-21 in these cells were all increased at 3 days post-injury [39]. miR-21 is also significantly upregulated in serum of severe TBI with extra-cranial injury patients at all time points after 4 h from injury, and may be a novel biomarkers for the diagnosis and prognosis of severe TBI [20]. More recently, studies showed that miR-21 is secreted from neurons as potential exosome vesical (EV) cargo after TBI [40]. The upregulation of expression levels of miR-21 after TBI indicated that it may participate in the pathological process.

miR-21 and Inflammation

Neuroinflammation is an adaptive response to tissue injury/infection that can also cause and worsen pathology in neurological disorders. Proinflammatory factors in the central nervous system (CNS) can be beneficial, and are critical to host defense [41]. However, neuroinflammation also has a "dark side"[42]. Pathological neuroinflammation occurs when the inflammatory response is exaggerated or persists long term, and is likely neurotoxic and causes secondary damage [43]. miRNAs is involved in the initiation and maintenance of neuroinflammation [44]. Key pro-inflammatory (miR-155, miR-27b, miR-326), anti-inflammatory (miR-124, miR-146a, miR-21, miR-223), and mixed immunomodulatory (let-7family) miRNAs have been discovered [22]. miR-21 is upregulated in neutrophils, dendritic cells, monocytes/macrophages, T cells, and affects their differentiation after neuroinflammation [45–48]. miR-21 could directly target PDCD4, participates in anti-inflammatory signaling by decreasing interleukin-6 (IL-6) and increasing IL-10 [49, 50]. Furthermore, Smad7 and Spry1 are also proved to be the targets of miR-21 that are relevant to neuroinflammation [51, 52]. Nevertheless, in Experimental Autoimmune Encephalomyelitis (EAE), miR-21 increased in T_h17 cells and promoted their differentiation by targeting Smad7, played a detrimental role [48]. miR-21 also has divergent roles in human Multiple sclerosis (MS), it is upregulated in cells from patients with Relapsing Remitting Multiple Sclerosis (RRMS) [53], but was downregulated in cells from patients with secondary progressive MS [54].

Overall, miR-21 plays an anti-inflammatory role in neurologic diseases, it also has detrimental effects in MS and other inflammatory conditions. But the role of miR-21 in inflammation after TBI remains unclear.

miR-21 and Neuronal Apoptosis

Neuronal apoptosis is one of the most crucial events after TBI [55]. The process of neuronal apoptosis can occur by multiple pathways [56]. Phosphatase and tensin homolog deleted on chromosome ten (PTEN) and p-Akt could protect neurons from damage induce-TBI [57]. Cleaved caspase-3, caspase-9, B-cell lymphoma-2(Bcl-2) and Bcl-2 Associated X Protein (Bax) are crucially the downstream apoptosis-related proteins of PTEN-Akt signaling pathway [58, 59]. While PTEN is an important target gene of miR-21 [60].

In experimental TBI model in vitro, the scratch cell injury of cortical neuron was transfected with miR-21 agomir/antagomir, the results showed that upregulation of miR-21 decreased the expression level of PTEN, and increased the phosphorylation of Akt significantly, meanwhile the downstream apoptosis-related proteins of PTEN-Akt signaling pathway were down-regulated [36]. In the fluid percussion injury rat model, intracerebroventricular infusion of miR-21 agomir or antagomir was used to manipulate the expression level of miR-21 in brain, the results showed that miR-21 inhibited the expression of apoptosis- related molecules, PTEN-Akt signaling pathway was also activated [39]. miR-21 binds to 3′-untranslated region of FasL, suppresses its expression in Primary microglial cells of Oxygen-glucose deprivation (OGD) condition. After addition of Soluble FasL (sFasL), neurons cultured in CM from resting microglia triggered apoptosis, overexpression of miR-21 can reverse this effect [61].Taken together, miR-21 can exert the function of reducing neuronal apoptosis through activating

the PTEN-Akt signaling pathway, and more researches are required to look for other targeted gene of miR-21 in TBI.

miR-21 and Astrogliosis

Astrocytes participate in the innate immune response of the brain and produce most inflammatory mediators generally associated with macrophages, such as nitric oxide (NO), prostaglandins (PGs), ILs, chemokinesand extracellular proteases [62]. After traumatic brain insults, the astrogliosis included proliferation [63], phenotypic changes [64] and cellular hypertrophy of astroglias. Reactive astrogliosis are increasingly recognized as potential targets for novel therapeutic strategies in TBI [65].

The expression levels of miR-21 in astrocytes were increased at 3 days after TBI [39], but the concrete role of miR-21 in astrogliosis after TBI has not been reported. Bhalala et al. reported that overexpression of miR-21 in astrocytes attenuated the hypertrophic response to Spinal Cord Injury (SCI), and inhibition of miR-21 function in astrocytes resulted in increased axon density within the lesion site. But, expression levels of PDCD4 and PTEN, which have been demonstrated as the important target genes of miR-21, were nearly unchanged [66]. The signaling molecules that activate the miR-21 response to astrogliosis may be adistinct set of yet unidentified gene targets.

miR-21 and Secondary Blood–Brain Barrier Damage

Blood brain barrier is a multicellular vascular structure, consists of brain endothelial cells, astrocytes, pericytes, neurons and extracellular matrix (ECM), that separates systemic blood circulation from the central nervous system. The integrity of BBB is essential for maintaining cerebral homeostasis. Blood–brain barrier disruption occur in the secondary injury that following TBI, which leads to neuroinflammation, cellular apoptosis and other secondary pathological events after TBI [67, 68]. Recently, BBB damage has been recognised as a potential key target in the future management ofTBI for its role in the development of cerebral edema.

In the scratch injury model of cultured brain microvascular endothelial cells (BMVECs), studies showed that upregulation of miR-21 in BMVECs suppressed inflammation by regulating the expression of inflammatory cytokines and nuclear factor-k-gene binding (NF-kB) signaling, inhibited cellular apoptosis by regulating the expression of apoptosis factors and Akt signal to alleviates leakage of injured brain microvascular endothelial barrier [69]. In the fluid percussion injury rat model, manipulating the expression level of miR-21 in brain exerted a protective effect on BBB by activating the Angiopoietin-1 (Ang-1)/Tie-2 (receptor of Ang-1) axis in BMVECs [70]. In conclusion, miR-21 can prevent BBB from damage after TBI.

miR-21 and Angiogenesis

Angiogenesis, formation of new capillariesfrom existing vessels, plays an important role in the functional recovery after TBI [71, 72]. Understanding the mechanisms of angiogenesis will be important for developing new therapies for brain injuries. Several putative mechanisms, like vascular endothelial growth factor (VEGF) [73, 74], the Wnt/β-catenin cascade [75], Ang-1 and Tie-2 axis [76] may be responsible to vascular repair after TBI.

miRNAs also play critical roles in angiogenesis [77], and can be classified into two groups, pro-angiogenic group and anti-angiogenic group. Among them, miR-21 is found to have pro-angiogenic effects [78, 79]. miR-21 inhibites the expression of PTEN, leading to activate Akt and ERK1/2 signaling pathways, and upregulate expression of VEGF and HIF-1α in regulating tumor angiogenesis [79]. Studies also show that miR-21 promotes angiogenesis after TBI by upregulating VEGF expression and activating Ang-1/Tie-2 axis in rates [39].

miR-21 and Physical Exercise

Physical exercise is an effective method in the management of TBI. The mechanisms may be that physical exercise improves cognitive function after TBI by inhibiting initiatory damage and secondary neuronal death, increasing the number of new neurons, improving neuronal plasticity, cognitive neural repair and behavioral rehabilitation [80, 81]. miRNAs have been involved in this process. Spontaneous Running Wheel (RW) improves cognitive deficits induced by TBI, altered expression of miR-21 and miR-34a in hippocampus are associated with this recovery process [81]. Studies also showed that miR-92a, miR-874 and miR-21 were involved in the therapeutic effect afforded by voluntary exercise in a TBI rat model [82]. miR-21 is upregulated after TBI, which then reduced by physical exercise. Over-expression of miR21 will reverse the beneficial effects induced by physical exercise by reducing spine density in hippocampus [83].

Conclusion

TBI leads to a complex series of pathological events after the primary insult including inflammation, neuronal apoptosis, reactive gliosis and disruption of blood brain barrier, which is known as secondary brain damage. Reducing

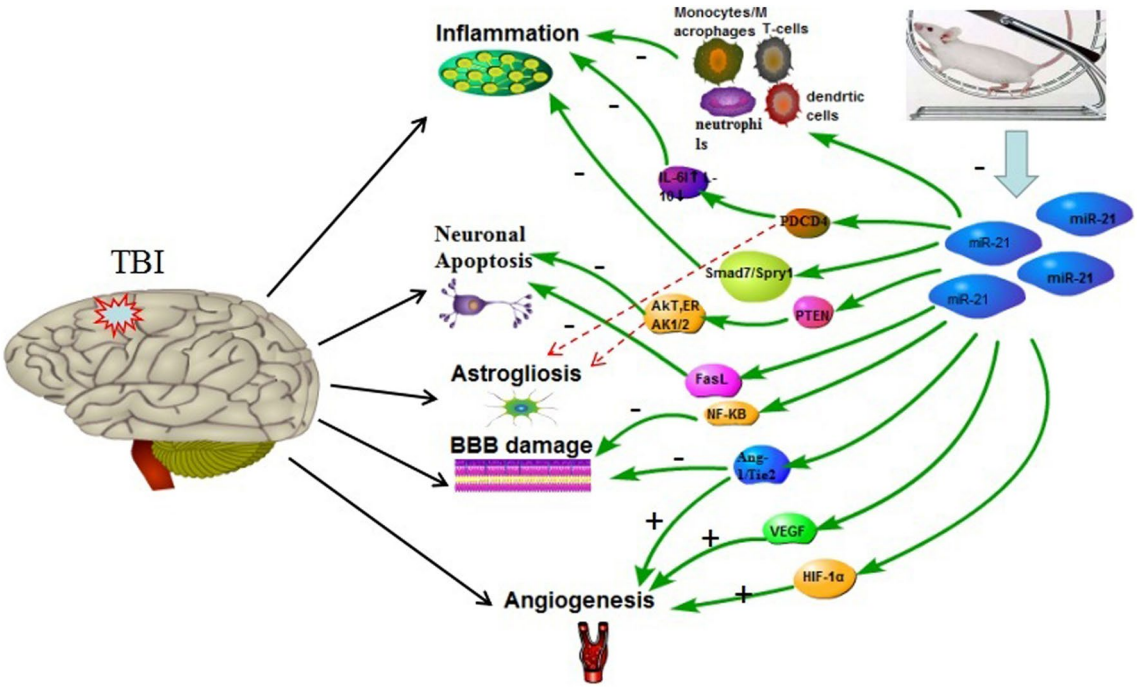

Fig. 1 The probable mechanisms of the effects produced by miR-21 on TBI. miR-21 affects the differentiation of neutrophils, dendritic cells, monocytes/macrophages and T cells, it directly targets PDCD4, Smad7 and Spry1, plays an anti-inflammatory role in neurologic diseases. Upregulation of miR-21 reduces neuronal apoptosis after TBI by decreasing the expression level of PTEN, and increasing the phosphorylation of Akt significantly, reducing the downstream apoptosis-related proteins of PTEN-Akt signaling pathway. The signaling molecules that activate miR-21 response to astrogliosis may be a distinct set of yet unidentified gene targets but not PDCD4 nor PTEN. miR-21 regulates the expression of NF-kB, the expression of apoptosis factors, Akt signal, excitation of Ang-1/Tie-2 axis, prevents BBB from damage after TBI. miR-21 promotes angiogenesis after TBI by upregulating VEGF expression and activating Ang-1/Tie-2 axis. miR-21 is upregulated after TBI, which then reduced by physical exercise. Over-expression of miR21 will reverse the beneficial effects induced by physical exercise

secondary brain damage can significantly improve the prognosis of TBI. miR-21 has been reported as an oncogene that functions as a regulator involved in cell proliferation, apoptotic cell death, inflammation. More and more studies show that miR-21 is involved in the pathogenesis of TBI. The probable mechanisms of the effects produced by miR-21 on TBI were illustrated in Fig. 1. The expression levels of miR-21 in various cells (neurons, astrocytes and microglias) of the CNS increased after TBI. The function of miR-21 in neuroinflammation is paradoxical. It directly targets PDCD4, Smad7 and Spry1, plays an anti-inflammatory role in neurologic diseases. It also has detrimental effects in MS and other inflammatory conditions. The role of miR-21 in neuroinflammation after TBI remains unclear. Upregulation of miR-21 reduces neuronal apoptosis after TBI by decreasing the expression level of PTEN, and increasing the phosphorylation of Akt significantly, reducing the downstream apoptosis-related proteins of PTEN-Akt signaling pathway. The signaling molecules that activate miR-21 response to astrogliosis may be a distinct set of yet unidentified gene targets but not PDCD4 nor PTEN. miR-21 regulates the expression of inflammatory cytokines, NF-kB signaling, the expression of apoptosis factors, Akt signal, excitation of Ang-1/Tie-2 axis, prevents BBB from damage after TBI. miR-21 promotes angiogenesis after TBI by upregulating VEGF expression and activating Ang-1/Tie-2 axis. Studies also show that miR-21 reduced by physical exercise, over-expression of miR21 will reverse the beneficial effects induced by physical exercise. miR-21 is now considered as a potential therapeutic target of TBI, further work is needed to elaborate the comprehensive mechanism underlying this process. At the same time, large-scale studies are required to evaluate the clinical values of miR-21 as a therapeutic target in TBI.

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Compliance with Ethical Standards

Conflict of interest No potential conflicts of interest were disclosed.

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