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REVIEWS

Non-coding RNAs and Exosomal Non-coding RNAs in Traumatic Brain Injury: the Small Player with Big Actions

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Abstract

Nowadays, there is an increasing concern regarding traumatic brain injury (TBI) worldwide since substantial morbidity is observed after it, and the long-term consequences that are not yet fully recognized. A number of cellular pathways related to the secondary injury in brain have been identified, including free radical production (owing to mitochondrial dysfunction), excitotoxicity (regulated by excitatory neurotransmitters), apoptosis, and neuroinflammatory responses (as a result of activation of the immune system and central nervous system). In this context, non-coding RNAs (ncRNAs) maintain a fundamental contribution to post-transcriptional regulation. It has been shown that mammalian brains express high levels of ncRNAs that are involved in several brain physiological processes. Furthermore, altered levels of ncRNA expression have been found in those with traumatic as well non-traumatic brain injuries. The current review highlights the primary molecular mechanisms participated in TBI that describes the latest and novel results about changes and role of ncRNAs in TBI in both clinical and experimental research.

Keywords Traumatic brain injury · Non-coding RNA · Exosome · Long non-coding RNAs · MicroRNAs

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Introduction

As defined by the experts, traumatic brain injury (TBI) is one of the injuries resulting from the mechanical external forces, which leads to the brief loss of consciousness or change in mental status [1]. It has been reported that near 50 million TBI cases occur each year; therefore, about 50% of worldwide population suffers from TBI throughout their lives [2]. TBI has been taken into account as the main cause of disability and mortality in the young adults in the UK [3]. Additionally, it was shown that TBI occurrence rate is much higher in non-high-income countries [2]. It imposes a great financial burden on healthcare system every year [2]. It is characterized by primary injury from an external mechanical force, and subsequent second injury refers to pathological changes that finally contribute to neuron cell death [4, 5].

Moreover, non-coding RNAs (ncRNAs) have been shown to be one of the families of RNAs, which cannot to be translated into proteins; however, they constitute the main part of the human transcriptome [6]. They categorized into two main groups based on their functions: housekeeping ncRNAs like transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), as well as small nuclear RNAs (snRNAs), and regulatory ncRNAs, such as PIWI-interacting RNAs (piRNAs), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs); nonetheless, despite the lack of comprehension knowledge about their physiological roles, other ncRNAs were once thought as transcriptional noise [7, 8]. Nonetheless, reports demonstrated that they maintain pivotal physiological as well as pathological roles via modulating translation [9, 10]. High levels of ncRNAs are expressed in mammalian brains, whereas emerging evidence claimed that acute as well as chronic central nervous system (CNS) damages can change the expression profiles of ncRNAs and their functions [11–17].

The present study provides a comprehensive review concerning the present knowledge on the role and function of ncRNAs in TBI.

MicroRNAs and Brain Trauma

MiRNAs are known as a group of ncRNAs which primarily involve in regulating post-transcriptional via and stimulating messenger RNA (mRNA) degradation [18]. For achieving post-transcriptional regulation, RNA-induced silencing complex (RISC) promotes interactions of mature miRNAs with a 3′ untranslated region of specific mRNAs [19]. Tremendous advancements in bioinformatic technology contributed to understating the pivotal role of miRNAs in TBI [20–22]. Emerging reports are in the support of the fact that miRNAs can be considered as biomarkers in a number of diseases related to neurology, including, but not limited to, Parkinson and TBI owing to its consistent human body fluids [23, 24].

NF-κB signaling pathways are taken into account as one of the leading signaling pathways which participated in inflammation, and scientists have found out that their activation is closely associated with complications of TBI [25]. The role of NF-κB signaling pathways and their inhibitors in TBI has been at the center of focus of recent studies. Great amount of attempts has been put forth to use these pathway inhibitors to reduce neuroinflammatory condition and ameliorate the consequences of TBI. For example, an in vivo study demonstrated that metformin exerted neuroprotective effects on TBI through prohibiting the NF-κB and MAPK signaling pathways [26]. Another experimental study declared that apocynin can protect the cerebral neuron against autophagy and enhance the memory and learning capabilities in rat model of TBI via prohibiting the TLR4/NF-κB signaling pathway [27]. Additionally, it was shown that NF-κB activation contributed to higher apoptosis and neuroinflammation in those with TBI [28].

Zhang et al. [29] designed a study to assess their hypothesis that miR-146a may be involved in progressing TBI. For that purpose, they established a TBI mouse model through the controlled cortical impact (CCI) injury. Researchers assessed these chemokine values via ELISAs but applied behavioral assays to evaluate the effect of miR-146a mimics on the neurological function. The investigators used western blot and qRT-PCR to determine the protein levels and the expression values of RNAs. The authors found enhanced levels of miR-146a in serum and brain and serum and its mimic reduced IL-6, tumor necrosis factor α (TNF-α) values, and IL-1β in brain through prohibiting NF-κB signaling pathways. Its mimic also ameliorated the brain injuries and enhanced the long-term learning and memory capabilities in mouse with TBI. In summer, miR-146a has a pivotal role in TBI-induced injuries by activation of the NF-κB signaling pathway [29].

Researchers also introduced calcium/calmodulin-dependent serine protein kinase (CASK) as one of the unique membrane-associated guanylate kinase (MAGUK) proteins which contains numerous domains that are involved in protein interaction. A high amount of CASK can be found in the central nervous system [30, 31]. A variety of functions is attributed to CASK, such as regulation of gene expression, neural development, and synapse formation [30–32]. It has been found out that synaptic transmission has a close correlation with several neurological functions like memory and learning so that its loss is associated with cognitive impairment [33, 34].

The alpha-synuclein (SNCA) protein has been known as one of the key components in Lewy bodies of those suffering from Parkinson disease and plays a mandatory contribution to this disease. According to the documents, its expression is modulated by miR-153 [35] and is highly expressed in presynaptic terminals [36–40]. SNCA upregulation is able to stimulate synaptic impairments including prohibition of neurotransmitter secretion and decrease in synaptic vesicle density [41, 42]. The levels of alpha-synuclein in the cerebrospinal fluid (CSF) have been shown to be enhanced in those with TBI, and this enhancement is attributed to secretion of the soluble alpha-synuclein from the damaged glial cells and neurons, as well as the cause of synaptic impairment and disrupt transportation in those with TBI [43, 44]. An experimental research revealed a transient enhance of alpha-synuclein in subcortical axons in an aged mouse model of TBI; nonetheless, this enhancement disappeared 4 months following TBI [45].

Liu et al. [46] made an effort to characterize dynamic miRNA expression profile in the ipsilateral hippocampus of TBI rat model. The investigators explored 156 miRNAs of which 10 were dysregulated significantly and continuously following TBI. Online program analyses demonstrated that these 10 miRNAs can regulate 107 genes, and thereafter, several related biological processes were explored using bioinformatic and gene ontology analyses. These miRNAs may have the potential to initiate explored biological processes. The overexpression of three of these 10 miRNAs (miR-144, miR-340-5p, and miR-153) following TBI established using qRT-PCR and downregulation of their targeted proteins, namely CASK, SNCA, and nuclear factor erythroid 2–related factor 2 (NRF2), has been also demonstrated. Collectively, miR-144, miR-340-5p, and miR-153 have been shown to have a crucial role in neurological complications following TBI and can be considered as the valuable target for neurological complications after TBI [46].

In addition, dual-specificity phosphatase 1 (DUSP1) has been known as a well-recognized phosphatase that participates in the activation of mitogen-activated protein kinase phosphatase 1 (MKP-1) [47]. According to the findings, DUSP1 has the potential to moderate the mitogen-activated protein kinase (MAPK) signaling, thereby modulating cell death and proliferation or rapid growth [48, 49]. MAPK-p38 is thought to maintain a pivotal role in cellular signal transduction pathways [50]. Emerging evidence revealed that MAPK-p38 participated in several cellular processes including transferring signals to the nucleus, modulating gene expression, and cell differentiation and proliferation [51]. A study revealed the prognostic value of MAPK family in osteosarcoma and DUSP1 capacity as a valuable candidate for this malignant tumor treatment [52].

Qi and Wang [53] designed an in vivo experiment to identify the contribution of miR-429 to microglia-induced inflammation after TBI. RT-PCR was employed to determine the miR-429 expression in microglia and LPS-activated microglia in TBI. A TBI model of mice was established for evaluating the impact of miR-429 prohibition on neurological damages and inflammatory responses. LPS and TBI were accompanied by overexpression of inflammatory cytokines, miR-429, MAPK-p38, and phosphorylated NF-κB in microglia. The prohibition of miR-429 led to improvements in neurological dysfunction of mice with TBI. Bioinformatic tests revealed that DUSP1 can be prohibited by miR-429, leading to phosphorylated NF-κB and MAPK-p38 inhibition. In summary, miR-429 is involved in pro-inflammatory responses of the activated microglia via affecting DUSP1. MiR-429 prohibition is associated with lower inflammatory cytokine production of microglia and neurological consequences following TBI [53].

Bcl2 family contains different proteins, which are involved in neuronal death following injuries, such as pro-survival proteins (for example, BclxL and Bcl2), BH3-only domain proteins (for example, PUMA, Noxa, Bim, and Bid), and pro-apoptotic multidomain (for example, Bak and Bax) [54]. BH3-only proteins provoke neuron death via inducing mitochondrial outer membrane permeability as well as secretion of cytochrome c and apoptosis-inducing factor 1 (AIF-1) [55, 56]. Moreover, BH3-only proteins were shown to be involved in neural loss following CNS damage [57], such as TBI [58, 59]. Conversely, Akt (protein kinase B) was shown to stimulate neuronal survival via phosphorylating pro-apoptotic proteins, especially forkhead box O3 (FoxO3) and glycogen synthase kinase 3β (GSK3β), which are proved to be initiators of the expression of BH3-only protein [60–62]. It has been shown that the prohibition of Akt signaling pathways contributes to FoxO3a activation and increases its proapoptotic target proteins, like Bim and PUMA expression [63, 64].

Sabirzhanov et al. [65] designed a study to examine whether modifications in expressing some miRNAs following TBI are able to activate cell death signaling pathways or not, which contribute to neuronal destruction and neurological impairments. A TBI model of mice was established using CCI. MiRNA arrays and qPCR were employed to identify the alteration in the expression of miRNAs until 72 h following TBI (Table 1). They found out that miRNA-711 was overexpressed in the cortex of TBI mice, and this overexpression was initiated 1 h, peaked 6 h, and lasted for 3 days following the injury. This overexpression was also detected in the in vitro TBI model. The investigators utilized miR-711 mimics to clarify the role of miRNA-711 in neural cell deaths. MiRNA-711 mimics applied were associated with enhanced neural cell deaths and caspase-3 activity in a concentration-dependent fashion. The inhibition of miRNA-711 significantly overexpressed Akt and its phosphorylated form, as well as GSK3 and its phosphorylated form. MiRNA-711

Table 1 MiRNAs and brain trauma

miRNA	Expression	Detection methods	Target	Model	Ref
miR-212-5p	Down	qRT-PCR	Ptgs2	In vivo, in vitro	[199]
miR-146a	Up	qRT-PCR	JNK, NF-κB	In vivo	[29]
miR-155	Up	RT-PCR	–	In vivo	[200]
miR-429	Up	qRT-PCR	DUSP1	Human, in vivo	[53]
miR-124-3p	Up	RT-PCR	DLL1	In vivo	[201]
miR-155	Up	RT-PCR	NOX2	In vivo	[202]
miR-93, miR-191, miR-499	Up	qRT-PCR	–	Human	[203]
miR-21-3p	Up	RT-PCR	MAT2B	In vivo, in vitro	[204]
miR-23a, miR-27a	Down	qPCR	Bcl-2	In vivo, in vitro	[205]
miR-136-3p, miR-9-3p	Up	RT-qPCR	–	In vivo, human	[206]
miR-155	Down	qRT-PCR	BACH1	In vivo	[207]
miR-21-5p	Up	qRT-PCR	PTEN	In vitro	[208]
miR-219a-5p	Up	RT-qPCR	CCNA2, CACUL1	Human, in vitro	[209]
miR-107	Down	qPCR	GRN	In vivo, in vitro	[210]
miR-145-3p	Down	RT-qPCR	NFATc2	In vivo	[211]
miR-124-3p	Up	RT-qPCR	–	In vivo	[212]
miR-193a	Up	RT-qPCR	NLRP3	In vivo, in vitro	[213]
miR-124-3p	Down	RT-qPCR	Stat3	In vivo, human	[214]
miR-34b	Down	RT-PCR	CRHR1	In vivo, in vitro	[215]
miR-433	Down	RT-qPCR	SPP1	In vitro, human	[76]
miR-711	Up	qPCR	Akt	In vivo, in vitro	[65]
miR-302	Down	qPCR	ERK1/2	In vivo, in vitro	[216]
miR-21, miR-92, miR-16	Up	qRT-PCR	–	Human	[217]
miR-133a-3p	Down	RT-qPCR	PSAT1	In vivo, human	[218]
miR-212/132	Up	qPCR	Cldn1, Jam3, Tjap1	In vivo, in vitro, human	[219]
miR-124-3p	Down	qRT-PCR	Plp2, Stat3	In vivo, human	[220]
miR-21	Up	qRT-PCR	PTEN	In vivo	[221]
miR-21	Up	qRT-PCR	SOD, CAT	In vivo	[222]
miR-30b-5p	Down	RT-PCR	SEMA3A	In vivo, in vitro	[223]
miR-3195, miR-328-5p	Up	RT-qPCR	–	Human	[224]
miR-34a, miR-451, miR-874	Up	qRT-PCR	Bcl2	In vivo, in vitro	[225]
miR-144, miR-153, miR-340-5p	Up	qRT-PCR	CASK, SNCA, NRF2	In vivo	[46]
miR-455-3p	Down	qPCR	HDAC2	In vivo	[226]
miR-203	Up	RT-qPCR	–	In vivo	[227]
miR-92a, miR-16	Up	qRT-PCR	–	Human	[20]
miR-21	Down	RT-PCR	PTEN, PDCD4, RECK, TIMP3	In vivo	[228]
miR-181c	Down	qRT-PCR	–	In vivo	[229]
miR-126	Up	qRT-PCR	EGFL7	In vivo, in vitro	[230]
miR-21, miR-92a, miR-874	Up	RT-qPCR	–	In vivo	[231]
miR-138, miR-124	Down	RT-qPCR	–	In vivo	[231]
miR-21, miR-124a, miR-107	Up	RT-PCR	IL-6, IL-1beta	In vivo	[232]
miR-200a-3p, miR-200b-3p	Up	ddPCR	–	In vivo	[233]
miR-450-3p, miR-194-5p	Down	ddPCR	–	In vivo	[233]
miR-21	Up	qRT-PCR	BCL-2, CBX4, FASLG	In vivo	[234]
miR-155, miR-223	Up	RT-qPCR	–	In vivo	[235]
miR-34a	Down	RT-PCR	Notch1	In vivo	[236]
miR-142-3p, miR-221	Up	qRT-PCR	p27	In vivo	[237]
miR-21	Up	qRT-PCR	PTEN	In vivo, in vitro	[238]
miR-139-5p	Down	qRT-PCR	NOTCH1	In vivo	[239]
miR-21	Up	qRT-PCR	–	In vivo	[240]

ddPCR droplet digital PCR

inhibition also reduced apoptosis markers including FoxO3a, cytochrome c, and AIF-1. In addition, authors observed that miRNA-711 inhibition was associated with enhanced Akt expression, reduced apoptosis and cortical lesion size, neuronal cell destruction in the hippocampus and cortex, and cognitive and motor dysfunctions. In conclusion, overexpression of miRNA-711 has a substantial role in neural destruction following TBI, through prohibition of Akt signaling pathways, indicating its potential as a valuable candidate for TBI treatment [65]. Additionally, a recent research demonstrated that overexpressed miR-219a-5p, which has been found in the neuronal cell injury model, prohibits cullin domain 1 (CACUL1) and cyclin-A2 (CCNA2) expression and regulates p53 and Akt signaling pathway, leading to an increase in levels of caspase-3 and promoting neural cell apoptosis [66]. In conclusion, since miR-219a-5p maintains its vital contribution to TBI development and pathophysiology, it has the potential to be considered as a valuable target for TBI treatment (Fig. 1) [66].

Osteopontin, also known as SPP1, is proved to be participated in inflammation, cancer development, and drug resistance [67]. SPP1 is capable to alter adhesion and rapid growth capacity of synovial cells by binding to the respective receptors over the synovial cells' surface [68]. Upregulation of SPP1 in the synovial fluid, articular cartilage, and synovium of those who are suffering from osteoarthritis was observed, and positive associations were found between SPP1 expression values and the severity of osteoarthritis [69, 70]. Bioinformatic assays revealed that miR-433 is a potent upstream mediator of SPP1 [71]. MiR-433 is a miRNA that has been demonstrated to be participated in some diseases. Enhanced expression of miR-433 expression appeared in three models of cardiac fibrosis [72]. MiR-433 was shown to be able to prohibit breast cancer cell proliferation via decreasing Rap1a expression and modulating the MAPK signaling pathway [73]. Besides, it has been unveiled that miR-433 has a crucial role in several malignancies including glioma and esophageal cancer [74, 75].

Han et al. [76] sought to evaluate SPP1 expression in tissues of tibial callus and heterotopic ossification of those with tibial fracture and TBI and assessed its interaction with miR-433. The TBI group was composed of 26 patients suffering from tibial fracture and brain injury, and the control group was composed of 26 patients suffering from only simple tibial fracture. Callus, heterotopic ossification tissues, and plasma of both groups were gathered to identify the SPP1 mRNA expression, protein, and miR-433. The authors applied qRT-PCR as well as western blot for measuring the miR-433 and SPP1 mRNA expression and SPP1 protein expression, respectively. Dual-luciferase reporter test was applied so as to clarify the direct interaction between SPP1 mRNA and miR-433. It was shown that TBI increased the incident formation of callus and heterotopic ossification in those suffering from fractures; nevertheless, TBI had no effect on the healing time of fracture. In the TBI group, enhanced levels of SPP1 mRNA and protein and also decreased levels of miR-433 compared to the control group were observed. MiR-433 was able to modulate SPP1 mRNA and protein expression through targeting the 3′-untranslated area of SPP1 mRNA. In conclusion, increased levels of

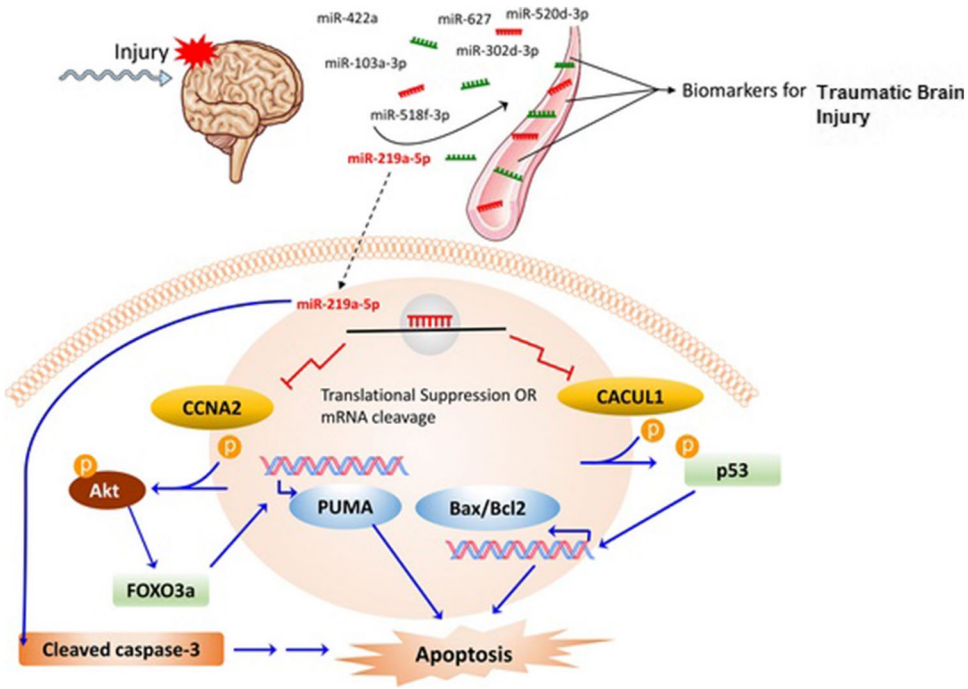

Fig. 1 The role of several miRNAs, which act as novel biomarkers for TBI, and the mechanism behind miR-219a-5p–induced neural cell apoptosis. Overexpression of several miRNAs, including miR-219a-5p, miR-103a-3p, miR-422a, miR-520d-3p, miR-302d-3p, miR-518f-3p, and miR-627, was found in TBI, and they are potentially applied as one of the valuable biomarkers to diagnose TBI. In the neuronal cell injury model, overexpressed miR-219a-5p prohibited CACUL1 and CCNA2 expression and regulated p53/Bcl-2 and Akt/Foxo3a signaling pathways, leading to enhanced neuronal cell apoptosis. This figure was adapted from Yan et al. [66]

protein and SPP1 mRNA were expected in tissues of callus, heterotopic ossification, and plasma of those with the tibial fracture and TBI, which may be because of decreased miR-433 expression [76].

LncRNAs and Brain Trauma

As mentioned earlier, lncRNAs have been introduced as one of the groups of ncRNAs known to be consisted of more than 200 bases [77]. Most of lncRNAs are processed alike to protein-coding messenger RNAs, such as 5′ end capping, splicing, and 3′ end polyadenylation [77, 78]. A growing bulk of evidence is in support of the fact that lncRNAs are involved virtually in all physiological cellular processes, including the expression of gene, activation of enzyme, and epigenetic modulation [79]. Although lncRNAs do not encode proteins, it was revealed that lncRNAs modulate gene expression at transcription, post-transcription, and epigenetic levels mostly through histone modifications, chromatin remodeling, and DNA demethylation [80, 81]. LncRNAs can increase or decrease the levels of target genes via binding to them or the employment of transcription factors [82, 83]. With the tremendous advancements in genome-wide techniques, some lncRNAs with the capacity of neurogenesis in adults have been explored, which confirmed the important functions of lncRNAs in the nervous system [84, 85]. According to several researches, the expression of lncRNAs is altered in brain injury; moreover, they may be participated in neurological consequences arise following brain injury [14, 86–94].

TNF-α is considered as one of the major triggers of cytokine secretion and an inducer of cell adhesion molecule expression, hence leading to progression of inflammation. It can modulate some of important cellular signaling pathways like JNK/AP-1 and IKK/NF-κB, thereby moderating the expression of downstream genes [95]. Moreover, TNF-α was shown to be capable of stimulating apoptosis; nonetheless, the exact mechanism is yet to be understood. It has been hypothesized that TNF-α may act with death ligands, including Apo2L/TRAIL and FasL to eliminate cells, which are infected with the pathogens. Furthermore, the other hypothesized mechanism is activating Bcl-2 gene and caspase families via stimulating JNK cascade [96].

Yu et al. [97] explored that lncRNA Gm4419 stimulated the apoptosis of astrocytes via TNF-α overexpression in an in vitro model of TBI. The authors found overexpression of Gm4419 in astrocytes following TBI. Gm4419 also was shown to be able to overexpress TNF-α expression and astrocyte apoptosis following TBI via targeting miR-466 l. Gm4419 served as the sponge for miR-466 l that is able to prohibit expression of TNF. Hence, throughout TBI, Gm4419 is able to overexpress the expression of TNF-α via binding to miR-466 l, contributing to neuroinflammation, neurological dysfunction, and the apoptosis of astrocytes. Altogether, this research provided a better insight of the mechanism by which Gm4419 stimulated neuroinflammation and neurological impairments in TBI [97].

Additionally, myeloid differentiation factor 88 (MYD88) adaptor protein has been known as a major member of the Toll-like receptor (TLR) and was revealed that it is involved in progression of diseases [98]. There is an evidence in support of the fact that MYD88 is highly overexpressed in an in vivo model of TBI, and its downregulation is capable of ameliorating TBI via decreasing microglial activation [99]. Moreover, its downregulation also can prohibit the secretion of inflammatory factors [100, 101]. Recently, great amount of interests has been driven toward roles of ubiquitin–proteasome systems in different diseases [102]. It has been demonstrated that E3 ubiquitin ligase mediates disease progression via modulating the ubiquitination of proteins [103]. Of note, Nrdp1, which is one of the members of E3 ubiquitin ligase family was demonstrated to be able to decrease the expression of MYD88 through regulating MYD88 ubiquitination [93].

Cheng et al. [104] illustrated lncRNA HOTAIR contribution to activation of microglia and inflammation responses in TBI in vivo. Therefore, LPS stimulation and Feeney's free-fall impact methods were recruited to establish an in vivo mouse model of TBI model and in vitro microglial activation, respectively. They also employed qRT-PCR in order to identify lncRNA HOTAIR expression in activated microglia. Then, they evaluated the microglial activation marker, namely Iba-1, and lncRNA HOTAIR expression levels utilizing qRT-PCR and the levels of inflammatory factors were measured utilizing western blot and ELISA. After that, RNA pull-down assay was employed by investigators to evaluate the association of lncRNA HOTAIR with MYD88 in vitro (Table 2). Additionally, researchers evaluated lncRNA HOTAIR effects on MYD88 stability by immunoprecipitation, ubiquitination, and cycloheximide (CHX) chase tests that determined MYD88 ubiquitination and detected overexpression of lncRNA HOTAIR in activated microglia. Its repression was associated with a significant decrease in microglial activation and secretion of inflammatory factors. It was shown that lncRNA HOTAIR was able to bind to MYD88 protein. Moreover, lncRNA HOTAIR upregulation was associated with increased MYD88 stability and prohibited Nrdp1-mediated ubiquitination of MYD88. Collectively, their findings revealed that lncRNA HOTAIR is upregulated in the activated microglia so that its repression was able to prohibit microglial activation and secretion of inflammatory factors through stimulating Nrdp1-mediated ubiquitination of MYD88 [104].

In addition, Nlrp3 inflammasome has been known as one of the major contributors to progression of inflammation

Table 2 Long non-coding RNAs and brain trauma

LncRNAs	Expression	Detection methods	Target	Model	Ref
Meg3	Up	qRT-PCR	miR-7a-5p	In vitro	[109]
Gm4419	Up	qRT-PCR	miR-466 l	In vitro	[97]
NKILA	Down	RT-qPCR	mir-195	In vivo, in vitro	[116]
GAS5	Up	qRT-PCR	miR-335	In vivo, in vitro	[241]
lncRpa	Up	qRT-PCR	miR-671	In vivo, in vitro	[242]
n333955, n332943, n335470, n341115	Up	qRT-PCR	–	Human	[243]
n381234	Down	qRT-PCR	–	Human	[243]
Zfas1	Up	qRT-PCR	NFKBIA	In vivo	[244]
ZFAS1	Up	qRT-PCR	–	In vivo	[245]
Neat1	Down	ChIP-qPCR	Pidd1	In vivo, in vitro	[246]
lncRNA2448-11, lncRNA1403	Up	RT-qPCR	TNF-α, IL-1β, TGF-β	In vitro, human	[247]
CRNDE	Up	RT-qPCR	GFAP, BrdU, NGF, nestin, NeuN	In vivo, human	[248]
HOTAIR	Up	qRT-PCR	MYD88	In vivo, in vitro	[104]
MEG3	Down	qPCR	TNF-α	Human	[249]
MALAT1	Up	qRT-PCR	EZH2	In vivo, in vitro	[128]
KCNQ1OT1	Up	RT-PCR	miR-873-5p	In vivo, in vitro	[250]

and its presence is mandatory for the release of inflammatory cytokines, which contribute to inflammatory responses [105–107]. The activation of NLRP3 inflammasome, which is initiated when they detect misfolded or aggregated amyloid-β, prion protein, α-synuclein, or superoxide dismutase, was shown to be associated with enhanced cleavage and caspase-1 and IL-1β secretion activity [105, 106]. The mentioned process is not restricted to microglia and can be found in other brain cells like astrocytes and neurons [105]. A body of evidence revealed that NLRP3 inflammasome was participated in the process of neurodegenerative disease [105]. Additionally, inhibition of activation and production of NLRP3 inflammasome can be a potential treatment for TBI patients [107]. It has been shown that Nlrp3 serves as one of the miR-7 targets in the primary microglia. Emerging evidence has shown that lncRNAs serve as the competing endogenous RNAs (ceRNAs) to prohibit miRNA activities and regulate the expression of mRNA, and imbalance of ceRNA networks leads to different diseases and progression of the diseases [108].

Meng et al. [109] sought to explore the mechanism Meg3 regulates inflammatory response and microglial activation in the in vitro TBI model. Investigators demonstrated that lipopolysaccharide in combination with ATP overexpressed Meg3, stimulated the activation of microglia and Nlrp3/caspase-1, and notably decreased miR-7a-5p. MiR-7a-5p upregulation was associated with decreased microglial activation stimulated by Meg3; nevertheless, its upregulation did not affect the expression of Meg3. Bioinformatic assays revealed that Meg3 serves as the target of miR-7a-5p that is able to decrease miR-7a-5p expression. Moreover, their findings reveled that Meg3 served as the ceRNA for miR-7a-5p. It also promoted microglial inflammation via modulating the expression of Nlrp3. Collectively, the current study elucidated that Meg3 modulates microglial inflammation via affecting the miR-7a-5p/Nlrp3 signaling pathway [109].

According to the research, NOD-like receptors (NLRs) have been introduced as the intracellular proteins involved in several defensive processes categorized into two groups: regulatory and inflammasome-forming NLRs. The inflammasome-forming NLRs have been known as components that are capable of starting the multiprotein inflammasome complex formation. Inflammasome formation improves the activation and maturation of IL-18 and IL-1β. To date, a number of research have been conducted to assess the inflammasome-forming NLRs in TBI. For instance, a number of clinical and experimental research have demonstrated that NLRP1 as well as NLRP3 have modulatory functions in TBI [110–112]. It has been reported that NLRX1 provokes reactive oxygen species formation so as to augment JNK and NF-κB signaling pathways [113]. An in vivo research provided an evidence that NLRX1 inhibits TBI progression via modulating the NF-κB signaling pathway [114]. Recently, a study found out that NLRX1 downregulation is able to modulate neuronal tissue insults following TBI [115].

He et al. [116] made an attempt to assess the role of the lncRNA-transmitted nuclear factor κB-interacting lncRNA (NKILA)-containing astrocyte-derived extracellular vehicles (EVs) in TBI. Therefore, in vivo and in vitro models of TBI were established utilizing mechanical damage to human

neurons and CCI, respectively. Researchers conducted gain-of-function and loss-of-function assays to identify NKILA, miR-195, as well as NLRX1 functions in damaged neurons in vitro. EVs were isolated from the NKILA-overexpressing astrocytes and applied for treating damaged neurons. They detected lower levels of NKILA expression in damaged neurons. Moreover, it was shown that NKILA can modulate NLRX1 expression via targeting miR-195. NKILA or NLRX1 upregulation was shown to be able to attenuate neuronal damages via apoptosis prohibition and stimulate neuronal proliferation. Astrocyte-derived EVs transferred NKILA into the neurons and contributed to NLRX1 overexpression, miR-195 downregulation, enhanced cell proliferation, and reduced cell apoptosis. They also revealed that NKILA-containing EVs exerted protective effects on brain injuries following TBI. In summary, astrocyte-derived EVs containing NKILA can ameliorate neural damages in TBI via binding to miR-195 and overexpressing NLRX1 [116].

As reported in a study, enhancer of zeste homolog 2 (EZH2) is recognized as one of the histone methyltransferases, which is able to decrease Krüppel-like factor 4 (KLF4) expression via targeting its promoter [117]. It was shown that KLF4 suppression has the potential to ameliorate neuronal injuries following TBI [118]. A report revealed that ischemic/reperfusion damage can lead to overexpression of EZH2 in microglia, whereas its prohibition modulates brain damage in an in vivo model of the brain injury induced by middle cerebral artery occlusion [119]. Additionally, EZH2 prohibition is able to attenuate neuroinflammation in rats with subarachnoid hemorrhage, emphasizing the importance of EZH2 prohibition in neural damages [120]. EZH2 was shown to be a core sub-unit of the polycomb repressive complex 2 (PRC2) that suppresses the gene transcription by its histone methyltransferase effects on lysine 27 (H3K27me3). Bulk of evidence exists in the support of the fact that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) employs PRC2 in order to increase H3K27me3 activity, leading to gene transcription suppression, mostly in malignancy and sepsis [121–124]. Despite that, recent reports revealed that EZH2 also can exert inhibition of gene transcription independent of activation of H3K27me3 [125–127].

Wu et al. [128] designed an in vivo and in vitro experiment to evaluate the contribution of MALAT1 to TBI. CCI was pertained to established a mouse model of TBI, and thus, researchers utilized oxygen–glucose deprivation as an in vitro model of TBI. Experiment findings demonstrated that MALAT1 suppression was associated with prohibition of endothelial cell viability and tube formation, while its silencing was associated with enhanced migration. They also illustrated that MALAT1 increased endothelial cell proliferation, functional vessel density, and cerebral perfusion in the injured areas following TBI. Bioinformatic tests showed that EZH2 serves as a downstream effector of MALAT1 in endothelial cells. Additionally, angiogenesis activities of MALAT1 were reversed by the activation of Jagged 1, the Notch homolog 1 (NOTCH1). Altogether, their findings clarified that MALAT1 maintains a mandatory role in angiogenesis following TBI via regulating the EZH2/NOTCH1 signaling pathway [128]. Figure 2 displays the various functions of lncRNAs in the pathophysiological of TBI.

Circular RNAs and Brain Trauma

Considering some studies in the field, circular RNAs (circRNAs) have been introduced as one of the novel groups of endogenous ncRNAs generated during splicing process [130, 131]. They were shown to be conserved and highly abundant in the brain [132, 133]. It has been shown that they participated in several biological processes such as translation and transcription regulation and served as miRNA sponges [10, 134–137]. Abnormal values of circRNAs have been observed in several diseases like heart diseases, neurodegenerative diseases, as well as malignancy [138, 139]. The expression of circRNAs was shown to be changed in those with TBI, indicating their potential for TBI management [140–143].

CXCR2, a G protein–coupled receptor, is shown to be involved in leukocyte recruitment from the circulation into locations of infection [144, 145]. Additionally, throughout neuroinflammation, CXCR2 participates in the activation of cerebral endothelial cells and, as a result, recruitment of leukocytes [146]. It also was shown to have a pivotal contribution to numerous inflammatory illnesses, including pancreatic inflammation [147], lung inflammation [148, 149], kidney inflammation [150], and skin inflammation [151].

Chen et al. [152] addressed whether circRNA expression near damage location in the mouse model of TBI is altered or not. A mouse model of TBI was established using a CCI model to cause brain trauma. The investigators extracted RNA from the cortex near the injury location so as to conduct RNA sequencing. In addition, 8036 circRNAs with differential expression have been detected of which 16 were significantly changed. Significantly enhanced levels of the circRNA chr8_87,859,283–87,904,548 were found in the cerebral cortex near the damage location following TBI. The mentioned circRNAs facilitated neuroinflammation via enhancing the expression of CXCR2 through the sponging mmu-let-7a-5p (Table 3). Therefore, these five circRNAs have detrimental impact on the neurological function improvement in mouse model of TBI [152].

Researchers found the generation of TNF-α and IL-1β at the site of inflammation primarily by monocytes and macrophages is capable of inducing neurite growth by glial cell line–derived neurotrophic factor [153]. Moreover, IL-1β was

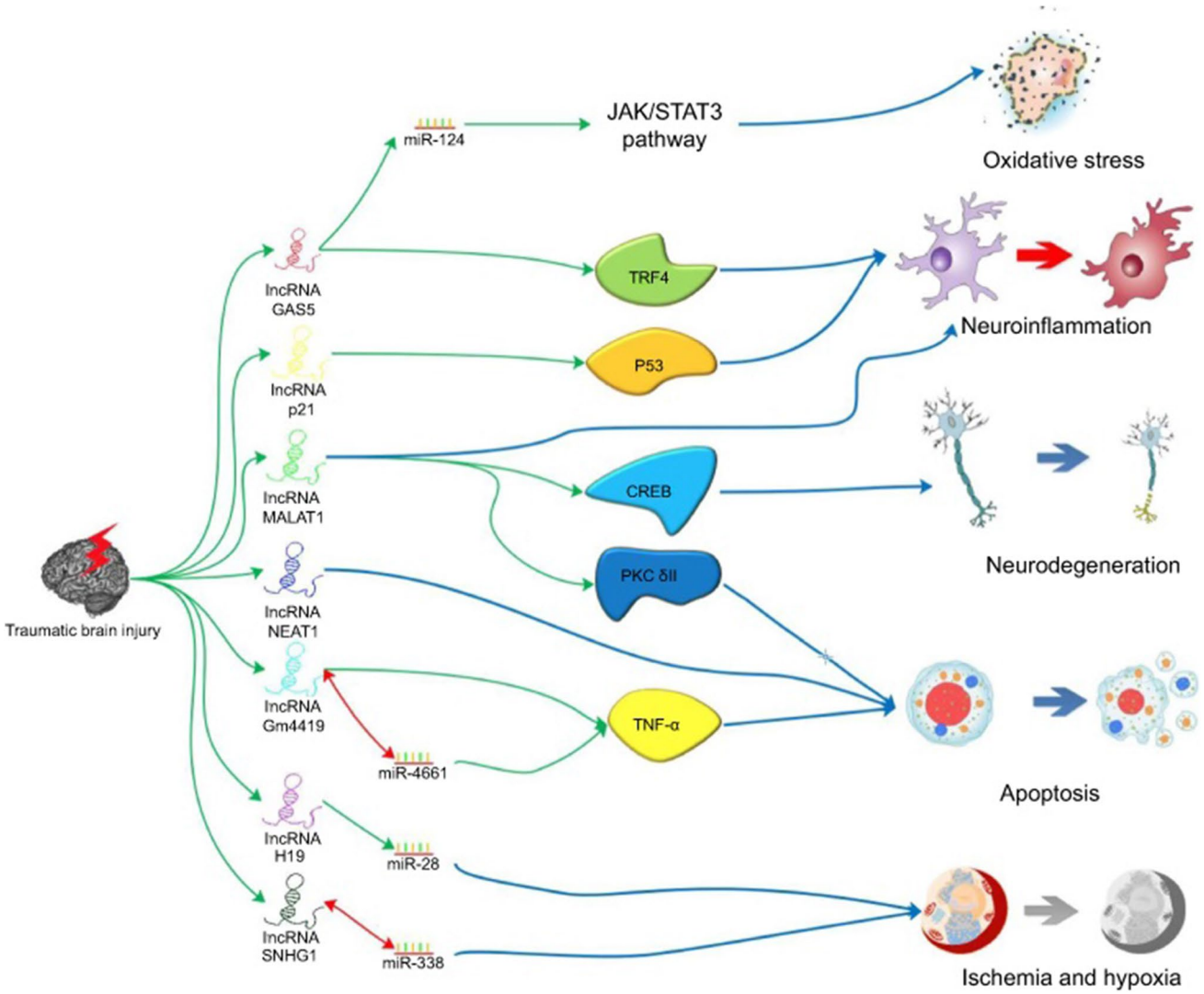

Fig. 2 The mechanisms involved in the effects of lncRNAs on TBI. Noteworthy, researchers identified several lncRNAs to maintain various fundamental contributions to the pathophysiology of TBI. GAS5 knockdown is associated with ameliorated RGC oxidative stress injury through overexpressing miR-124. GAS5 is able to prohibit microglial M2 polarization via blocking TRF4 transcription. LincRNA-p21 can induce the activation of microglia via a p53-dependent transcriptional pathway. Additionally, lncRNA MALAT1 is involved in astrocyte apoptosis and neurodegeneration through alternative splicing of PKC δII and CREB signaling pathway. Moreover, there was a relationship between astrocyte apoptosis and the nuclear enriched abundant transcript 1 (NEAT1) and Gm4419 in which Gm4419 may act as a sponge for miR-466 l to target TNF-α. In addition, H19 has the capability to ameliorate hypoxia-induced damage via downregulation of miR-28 expression. Finally, SNHG1 can prevent hypoxia and the secondary cerebral ischemia through sponging miR-338. This figure was adapted from Li et al. [129]

revealed to have dual opposite effects on neurons [154–156]. The findings of an in vitro study suggested that IL-1β exerts its neuroprotective effects through prohibiting N-type Ca^{2+} channel protein expression, leading to deactivation of N-type Ca^{2+} channels [157]. Intraparenchymal injection of IL-1β into the medial forebrain bundle largely reduced the number of dopaminergic neurons in striatum [158]. Conversely, IL-1β was shown to have the potential to promote the apoptosis of neurons via altering the expression activity of the p38 mitogen–activated protein kinase and caspase-3 in rats following spinal cord injury [159]. An in vitro investigation illustrated that IL-1β is important for promoting neural precursor cell apoptosis and cell cycle arrest [156]. Additionally, emerging evidence demonstrated that JAK2/STAT3 signaling pathway activation and IL-1β generation are dependent on the inhibitor of the cytokine signaling 1 (SOCS-1) downregulation and STAT3 phosphorylation, respectively [160, 161].

As stated in a study, oxygen–glucose deprivation (GOD)-activated microglia promote apoptosis by secreting several

Table 3 Circular RNAs and brain trauma

Circular RNAs	Expression	Detection methods	Target	Model	Ref
circRNA-04218	Up	qRT-PCR	–	In vivo	[140]
circRar1	Up	qRT-PCR	miR-671	In vivo, in vitro	[242]
circ-PTK2	Up	RT-PCR	miR-29b	In vivo, in vitro	[162]
circRNA chr8_87,859,283–87,904,548	Up	RT-qPCR	mmu-let-7a-5p	In vivo, in vitro	[152]
circLrp1b	Up	qRT-PCR	miR-27a-3p	In vivo	[169]
rno_circRNA_001167, rno_circRNA_001168	Down	qRT-PCR	–	In vivo	[142]
rno_circRNA_006508, rno_circRNA_010705	Up	qRT-PCR	–	In vivo	[142]

cytokines and several miRNAs may regulate this process. Wang et al. [162] designed a study to evaluate how circPTK2 and miR-29b expression can affect the OGD-activated microglia-induced neuronal apoptosis in vitro. The authors demonstrated enhanced IL-1β and TNF-α as well as lower levels of miR-29b in OGD-activated microglia. In addition, miR-29b prohibited OGD-activated microglia-induced neuronal apoptosis. Moreover, miR-29b could augment and reduce SOCS-1 expression and JAK2/STAT3 signaling, respectively. Furthermore, JAK2/STAT3 prohibition was associated with lower levels of IL-1β, whereas overexpression of miR-29b or SOCS-1 was associated with lower levels of IL-1β. In fact, IL-1β has been demonstrated to be involved in the hippocampal neuron apoptosis. Additionally, both SOCS-1 overexpression and prohibition of JAK2/STAT3 signaling pathway can inhibit OGD-activated microglia-induced neuronal apoptosis, indicating miR-29b prohibits OGD-activated microglia-induced neuronal apoptosis through stimulating SOCS-1 expression, prohibiting JNK2/STAT3 signaling pathway and IL-1β expression. They also showed that circPTK2 was capable of modulating microglia-induced neuronal apoptosis via serving as an inhibitor of miR-29b [162].

As stated in the research, DNA damage–regulated autophagy modulator protein 2 (DRAM2) encodes 6 transmembrane domains and a protein with 266 amino acids [163]. This protein has been identified as a lysosomal protein involved in autophagy activation [164]. HOTAIRM1 maintains a vital contribution to modulation of autophagy pathways via PML-RARA degradation. HOTAIRM1 serves as the miRNA sponge in the pathway containing miR-20a, miR-106b, and miR-125b-5p as well as the respective targets DRAM2, E2F1, and ULK1 [165]. The gene can act as an autophagy modulator via acting as a potential target of miR-125b-1 [166]. It was also revealed that human miR144* through targeting DRAM2 is able to prohibit immune responses to *Mycobacterium tuberculosis* [167]. Moreover, Bai et al. [168] observed miR-125b-5p, which is overexpressed in retinoblastoma, via suppressing DRAM2 which enhances retinoblastoma cell invasion and proliferation.

Treatment with dexmedetomidine (DEX) was associated with favorable outcomes in those with TBI, which was mediated by prohibiting NLRP3/caspase-1. Li et al. [169] designed an in vivo study to evaluate the role of circLrp1b in DEX-mediated TBI of brain and underlying mechanism in those with TBI. A rat TBI model was developed via CCI to induce brain trauma. Thereafter, rats were given intracerebroventricular injections of lentiviral vector and then intraperitoneal injection of DEX. Therefore, DEX treatment was shown to be able to improve TBI-induced autophagy, inflammation, and neurological deficits in vivo, associated with overexpression of Dram2 and circLrp1b and miR-27a-3p downregulation. It was demonstrated that these effects were augmented by combined treatment with circLrp1b, which were reversed by miR-27a-3p prohibition or Dram2 upregulation. CircLrp1b can enhance the expression of Dram2 through acting as a sponge for miR-27a-3p in order to stimulate TBI-induced autophagy that is attenuated by administration of DEX. Altogether, this research declared that DEX is able to prohibit TBI-induced autophagy and inflammatory responses via inhibiting the circLrp1b/miR-27a-3p/Dram2 signaling pathway [169].

Ferroptosis is a non-apoptotic type of regulated cell death which is highly dependent on iron and has drawn a quite amount of attention due to its role in TBI. Its role in TBI has been demonstrated; however, the exact mechanism is yet to be clear [170]. Besides, it is widely accepted that melatonin has a neuroprotective property [171]. Nevertheless, researchers did not clarify the antiferroptotic impacts of melatonin on TBI. Very recently, Wu et al. [172] dealt with the evaluation of ferroptosis expression following TBI, and melatonin administration can be used as a protective agent against endoplasmic reticulum (ER) stress and ferroptosis following TBI. The authors reached out that the levels of lipid peroxidation increased following TBI, whereas melatonin treatment led to the improvement of the TBI-induced neurological deficits and sleep disorders in TBI mice. Furthermore, melatonin treatment was able to decrease lipid peroxidation and iron accumulation, leading to ameliorated ER stress and ferroptosis. Moreover, authors found upregulation and downregulation of 905 and

921 circRNAs in brain tissues collected from TBI mice treated with melatonin. They found that melatonin treatment is associated with lower values of circPtpn14, which was shown to be positively associated with ferroptosis-related 5-lipoxygenase (5-LOX) expression. Furthermore, circPtpn14 upregulation eliminated prohibitory impacts of melatonin on ferroptosis. Altogether, the investigators suggested that melatonin exhibits its anti-ER stress and antiferroptotic impacts on TBI via ameliorating lipid peroxidation by the circPtpn14/miR-351-5p/5-LOX signaling pathway (Fig. 3) [172].

Exosomal miRNAs and Brain Trauma

Exosomes are small EVs that can be released by lots of various types of cells and are categorized into three major groups based on their size. They can communicate with the remaining cells on the surface of the cell through cell receptors or release their contents including protein, lipids, as well as nucleic acids into the cell cytoplasm through endocytosis. Since exosomes release protein, lipids, and nucleic acids into recipient cells, they essentially contribute to many physiological and pathophysiological cellular processes [173, 174]. However, there has been growing interest toward the roles of exosomes miRNA in TBI [175]. Figure 4 exhibits the neuroprotective and neuroinflammatory impacts of EVs on TBI [176].

Rab GTPases, which are encoded by a group of more than 60 human genes, are known as important regulators of intracellular trafficking processes [177]. Rab11 is a member of Rab GTPase family. It was shown that Rab11 participated in the early as well as late phase of autophagy and has a fundamental role in autophagosome maturation [178–180]. Rab11 was shown to participate in interactions of multivesicular bodies with autophagic pathways in K652 cells [181]. Recycling endosomes (REs) serve as a provider of membrane for autophagosome biogenesis, and Rab11 may be involved in transporting vesicles to the location of autophagosome formation [182, 183]. A research revealed that Rab11 probably simplify binding the autophagosomes and endosomes via eliminating hook from mature late endosomes [184]. Recent evidence claimed that Rab11a, which is a subgroup of Rab11, maintains a mandatory role in autophagy. In 2018, a study demonstrated that Rab11a-positive membrane is an essential component for autophagosomes to evolve and its loss disrupts the assembly and recruitment of autophagic machinery. Figure 4 was adapted from Puri et al. [185].

Li et al. [186] designed an experimental research to evaluate the potential and underlying mechanism of exosomal miR-21-5p treatment in TBI. Brain extracts were isolated from a repetitive TBI (rTBI) mouse model and were applied to cultured HT-22 neurons to mimic the microenvironment of TBI in vitro. Exosomes were purified using ultracentrifugation, and their characteristics were determined, utilizing transmission electron microscopy and NanoSight technology. The authors

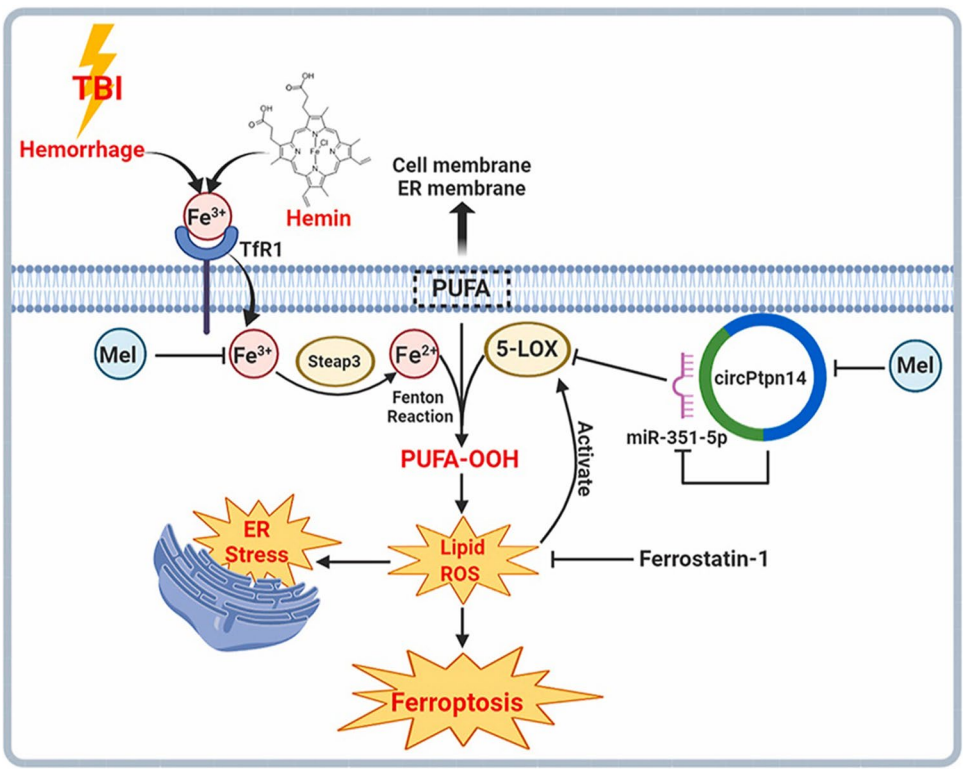

Fig. 3 The mechanism behind antiferroptotic and ER stress properties of melatonin in TBI. Intracranial hematoma following TBI contributes to the entrance of free-iron ions to the cell via TfR1. As mentioned earlier, the intracellular divalent iron ions are capable of catalyzing the production of lipid peroxides by reaction of Fenton. Therefore, lipid peroxide accumulation results in ferroptosis and ER stress. Melatonin is able to pass the cell membranes and BBB easily. It can immediately chelate the free-iron ions to inhibit the lipid peroxidation. Moreover, melatonin can indirectly decrease the expression of 5-LOX via suppressing circPtpn14 expression, leading to accumulation of reducing lipid peroxide and prohibition of ferroptosis and ER stress. This figure was adapted from Wu et al. [172]

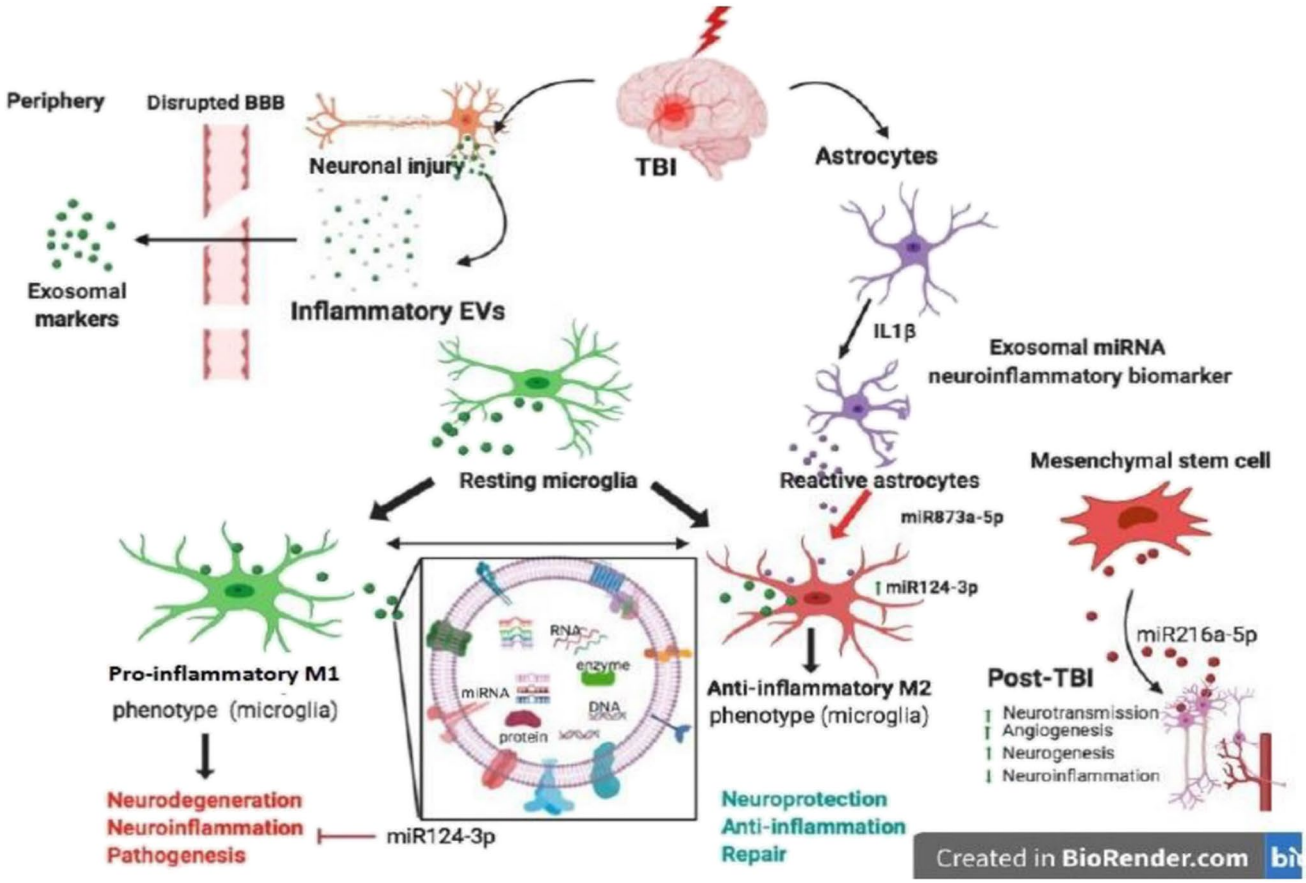

Fig. 4 Impact of EVs on the traumatic brain injury

developed an in vitro model of TBI to evaluate the impacts of the miR-21-5p administration on neuron autophagy. Furthermore, miR-21-5p expression is enhanced in exosomal neurons following rTBI mouse brain extract treatment. Higher levels of autophagy were detected in an in vitro model of TBI (Table 4). Treatment with exosomal miR-21-5p had the potential to prohibit autophagy via enhancing the miR-21-5p level in damaged neurons. MiR-21-5p by targeting the translational site of Rab11a suppressed Rab11a expression, thereby inhibiting Rab11a-induced autophagy. Altogether, higher values of miR-21-5p can be detected in chronic TBI compared to acute TBI. Exosomal miR-21-5p exerts its protective effects via prohibiting autophagy by targeting Rab11a in rats with TBI [186].

According to the studies, brain-derived neurotrophic factor (BDNF) has been known as one of the neurotrophic factors that maintain a mandatory contribution to neuron survival, axonal sprouting, and regeneration in response to TBI [187]. As a result, several experimental and clinical researches assessed BDNF impacts on TBI recovery [188, 189]. BDNF was introduced as the most broadly distributed neurotrophin in the CNS, participating in plenty of facets of brain function, including neuron survival, differentiation, and synaptic

Table 4 Exosomal miRNAs and brain trauma

Cargo	Detection methods	Target	Model	Ref
miR-124-3p	RT-PCR	PDE4B	In vivo, in vitro	[251]
miR-124	RT-PCR	TLR4	In vivo, in vitro	[252]
miR-124-3p	qRT-PCR	Rela	In vivo, in vitro	[253]
miR-873a-5p	qRT-PCR	ERK, NF-κB	In vivo, in vitro, human	[254]
miR-21-5p	RT-PCR	–	In vivo, in vitro	[255]
miR-21-5p	RT-PCR	Rab11a	In vivo, in vitro	[186]
miR-219	RT-PCR	–	In vivo	[256]
miR-216a-5p	qRT-PCR	NEUROG2	In vivo, in vitro	[198]

plasticity [187, 190, 191]. It is able to stimulate the neuron growth and decrease neuron death, provoking differentiation of the neural stem cells and MSCs into the neurons [192–194]. It exerts its impacts via tyrosine kinase receptor B (TrkB) [195]. It has been shown that TBI and spinal cord injury lead to upregulation of TrkB mRNA at TBI as well as spinal cord injury [196, 197].

It was unveiled that injecting exosomes extracted from the mesenchymal stromal cells (MSCs-Exo) is associated with better neurological function in those with TBI. Xu et al. [198] made a hypothesis that treatment with BDNF-stimulated MSCs-Exo may improve neurological function and neuron regeneration in a rat model of TBI. Then, researchers isolated MSCs from the bone marrow of rats and added them to BDNF, the supernatant was gathered, and exosomes were isolated and purified by hypercentrifugation. The properties of exosomes were determined using western blot, transmission electron microscopy, and particle size analysis. The authors demonstrated that a BDNF-stimulated MSCs-Exo group was significantly better than a MSCs-Exo group in terms of spatial learning capability and regaining of sensorimotor function. Treatment with BDNF-stimulated MSCs-Exo prohibited the inflammation and provoked neurogenesis in rats and in vitro. The investigators also found out that miR-216a-5p was expressed in significantly higher levels in the BDNF-stimulated MSCs-Exo group relative to the MSCs-Exo group, and the function of miR-216a-5p is alike to BDNF-stimulated MSCs-Exo. Briefly, treatment with BDNF-stimulated MSCs-Exo has the potential to improve neural regeneration and inhibit neural apoptosis, which is thought to be owing to miR-216a-5p expression [198].

Conclusion

The incidence of TBI, known as a deleterious condition, is increasing globally. The mechanisms involved in secondary brain damage are profoundly complex, and the mechanisms involved in TBI are not yet fully clear. NcRNAs are known as a group of diverse RNA, which are classified into 2 main groups including regulatory and housekeeping ncRNAs. It has been shown that they are expressed in the brain at high levels and may be pivotal for some of brain functions and neurodevelopment. Lots of experimental and clinical research has demonstrated that expressing different ncRNAs was modified after TBI. Additionally, it has been unveiled that they may be involved in the pathophysiology of TBI and its related complications. Moreover, several studies have evaluated the diagnostic and prognostic significances of various ncRNAs and found that they could be utilized as one of the biomarkers for TBI discrimination and diagnosis in the future, given that it is not possible to completely clarify the function of non-coding transcripts out of a physiological context, especially because they are poorly conserved between species, making the in vivo experiments not easily translatable for applications in humans, and because, if compared to coding genes, they are more difficult to be explored. A lot of novel ncRNAs are completely uncharacterized by making the understanding of their role more complex. Besides, since they have a crucial role in TBI development and pathophysiology, they may be considered as a possible target for TBI treatment.

Author Contribution H. M. was involved in the conception, design, statistical analysis, and drafting of the manuscript. O. M., M. H., F. M., A. J. Y., A. O., A. S., S. S. T. Z., G. O. S., S. A. T. Z., M. R. H., and A. H. contributed in the data collection and manuscript drafting. All authors approved the final version for submission.

Data Availability The primary data for this study is available from the authors on request.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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