

The role of long noncoding RNA in traumatic brain injury

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Abstract: Traumatic brain injury (TBI), a mainly lethal and highly debilitating condition, is increasing worldwide. However, the underlying mechanism has not been fully elucidated and effective therapy is needed. Long noncoding RNAs (lncRNAs), which form a major class of noncoding RNAs, have emerged as novel targets for regulating physiological functions and mediating numerous neurological diseases. Notably, gene expression profile analyses have demonstrated aberrant changes in lncRNA expression in the cerebral cortex and hippocampus of rats, mice and human after TBI. lncRNAs may be associated with multiple pathophysiological processes following TBI and might play a crucial role in complications of TBI, such as traumatic optic neuropathy due to the regulation of specific signaling pathways. Some lncRNAs have also been found to be therapeutic targets for motor and cognitive recovery after TBI. lncRNAs may be promising biomarkers for TBI diagnosis, treatment, and prognosis prediction. However, further research is needed to clarify the underlying mechanisms and therapeutic effects of lncRNAs on TBI. We review the current progress of studies on lncRNAs in TBI to draw more attention to their roles in this debilitating condition.

Keywords: long non-coding RNA, traumatic brain injury, neuropathy

Introduction

In recent years, the incidence of traumatic brain injury (TBI) is increasing as a result of general use of motor vehicles, sports and falls, making it the leading cause of death and disability worldwide.^{1,2} It brings heavy emotional and economic burdens to individuals, families, and society. TBI survivors usually face a series of problems, such as epilepsy, motor and sensory disturbances, cognitive and neuropsychological dysfunction.³ Although the pathophysiological mechanism of TBI is known to be associated with primary damage of shearing and tearing forces, and secondary damage, the exact mechanism is still unclear.^{4,5} Secondary damage frequently occurs several minutes or months after TBI, and results in persistent neurological impairment. Generally, secondary damage is regulated by related pathways of glutamate excitotoxicity,^{6,7} free radical generation,⁸ and neuroinflammation,⁹ which contribute to oxidative stress, inflammation, neuronal apoptosis and other biochemical changes. Current treatment consists mainly of early detection, symptoms control, supportive therapy, and functional rehabilitation. However, the prompt prevention of secondary injury and effective treatment measures for satisfactory recovery are still lacking.¹⁰

A variety of noncoding RNA genes exists in the human and rodent genomes, such as ribosomal RNAs, transfer RNAs, small nuclear RNAs, microRNAs (miRNAs), and long noncoding RNAs (lncRNAs). It was gradually recognized that miRNAs were differentially expressed after TBI and would be novel biomarkers for the diagnosis, treatment, and prognosis prediction of such injury.¹¹ For example, Di Pietro et al¹² analyzed the expression miRNAs in serum of five mild

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TBI with extracranial injury patients, five severe TBI with extracranial injury patients and five healthy volunteers at different times post injury. They identified two miRNAs (miR-425-5p, miR-502) as ideal candidates for diagnosis of mild TBI and two miRNAs (miR-21 and miR-335) as valid biomarkers for diagnosis of severe TBI. As a large type of noncoding RNAs, lncRNAs have been emerging as important regulators of multiple disease processes.¹³ However, the functional significance of lncRNAs in TBI and their underlying mechanisms are less known compared with those of miRNAs. In this review, we summarize current knowledge about the roles of lncRNAs associated with TBI, which would help in the search for new therapeutic strategies.

Overview of lncRNAs

Biology of lncRNAs

As nonprotein-coding transcripts, noncoding RNAs account for at least 98% of the total human genome.¹⁴ They can be classified into miRNAs, P-element-induced wimpy testis (PIWI)-interacting RNAs, small nucleolar RNAs, lncRNAs and other types of ncRNAs.¹⁵ lncRNAs constitute the largest portion of the mammalian noncoding RNAs.¹⁶ Once regarded as transcriptional noise, increasing evidence has demonstrated that lncRNAs have multiple domains that can bind to DNA, RNA, and protein, modify the chromatin status, regulate transcription and translation, and ultimately affect gene expression.¹⁷ Although the functions of lncRNAs have not been completely decoded, studies have shown that they play different roles in cell proliferation, survival, and migration, as well as in maintaining genomic stability through guidance, bait, scaffolds and signaling molecules.^{18,19}

lncRNAs and neurological diseases

lncRNAs are highly expressed in the central nervous system (CNS).²⁰ Their aberrant expression has been confirmed to be related to neurodegenerative diseases, ischemic cerebrovascular diseases, gliomas and other neurological diseases. Using a triple transgenic mouse model of Alzheimer's disease, Lee et al²¹ identified 205 dysregulated lncRNAs from 4622 lncRNAs that would facilitate the process of molecule-targeted therapy. Kraus et al²² studied 30 brain specimens derived from 20 patients with Parkinson's disease (PD) and 10 controls and revealed that five lncRNAs were significantly differentially expressed. The five lncRNAs were H19 upstream conserved 1 and 2

(which was downregulated), and long intergenic noncoding RNA p21 (lincRNA-p21), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), small nucleolar RNA host gene 1 (SNHG1), and tiny noncoding RNA (which were all upregulated). Zhang et al²³ found that the knockout of lncRNA MALAT1 in a mouse model of oxygen and glucose deprivation (OGD) led to the significantly aggravated expression of proapoptotic factors and proinflammatory cytokines, which indicated that MALAT1 may have a protective role in ischemic stroke. MALAT1 was also thought to decrease the sensitivity of resistant glioblastoma.²⁴ Although many studies have recently reported the potential value of lncRNAs in neurological diseases, the topic is still in its infancy, especially on their roles in TBI.²⁵

lncRNAs in traumatic brain injury

lncRNA expression profiles in brain tissue of animal models and humans

lncRNA microarrays, RNA-sequencing (RNA-Seq), and bioinformatic analysis are commonly used to explore the expression of lncRNAs and delineate their molecular functions. To date, two studies in particular have reported the alteration of lncRNAs in mice or rats after TBI. Zhong et al²⁶ detected alterations in lncRNA and messenger RNA (mRNA) expression levels by high throughput sequencing in the mouse cortex at 24 hours postTBI, using a controlled cortical impact model. In a total of 64,530 transcripts including 27,457 transcripts identified as mRNA and 37,073 transcripts identified as lncRNA, 1,580 mRNAs and 823 lncRNAs were found to be significantly altered. Of the abnormally changed lncRNAs, 667 were upregulated and 156 were downregulated ($|\log_2(\text{fold change})| > 1$, $P < 0.05$). The good reproducibility and reliability of the RNA-Seq were confirmed by using the reverse transcription polymerase chain reaction. Their bioinformatic analysis showed that the mRNAs were mainly associated with inflammatory and immunological activities, metabolism, neuronal, and vascular networks. They also demonstrated the cross association between lncRNAs and mRNAs. Wang et al²⁷ performed a microarray analysis to profile lncRNAs that were altered in the rat hippocampus after TBI. A total of 271 lncRNAs and 1046 mRNAs were differentially expressed. Similarly, gene ontology (GO) and pathway analyses suggested that the alterations were related to inflammation, apoptosis, and necroptosis. The top three differentially expressed lncRNAs were: NR_002704, ENSRNOT00000062543, and Zfas. The

study proposed that the aberrantly expressed lncRNAs might regulate secondary injury through the mitogen-activated protein kinase signaling pathway, p53 signaling pathway, or cytokine-cytokine receptor interaction. However, their deduction deserves further validation. Moreover, when considering that secondary injury after TBI is a dynamic pathophysiological process,²⁸ the time-dependent changes of lncRNAs at different phases after TBI (eg, at 1 hour, 6 hours, 3 days, or 7 days) need to be clarified.

Yang et al²⁹ investigated the expression profiles of lncRNAs in human TBI, where three patients (two females and one male) were enrolled in the study. The samples analyzed were derived from contusion tissue and tissue adjacent to the contusion, both in the temporal and frontal lobes of the brain. Arraystar Human lncRNA Microarray version 2.0 (Aksomics, Shanghai, China) was designed for global profiling of human lncRNAs and protein coding transcripts. They found 43 upregulated and 56 downregulated lncRNAs, and concluded that the lncRNA and mRNA expression levels were significantly different between the injured site and surrounding tissue. In terms of the differences according to gender and the brain lobe sampled, the analytical methods needed to be more standardized and validation studies should be carefully carried out. Nevertheless, it is known that the genes of mice are different from those of humans, and the research thus confirmed that the roles lncRNAs play in the pathogenesis of TBI still need to be elucidated.

lncRNAs in the pathophysiological process of traumatic brain injury

TBI triggers complex pathophysiological processes,³⁰ where neuroinflammation is prominent in both the primary and secondary injury.³¹ As the immune cells of the brain, microglia actively respond to changes in the CNS environment. Sun et al³² observed that human lncRNA growth arrest-specific 5 (lncRNA GAS5) suppressed the transcription of terminal nucleotidyltransferase 4 (TRF4; a key factor that control M2 macrophage polarization), by recruiting polycomb repressive complex 2 (PRC2), thereby inhibiting microglial M2 polarization. Human lincRNA-p21 has also been reported to promotes microglial activation through a p53-dependent transcriptional pathway.³³ These studies provide valuable insights into the role of lncRNAs in the neuroinflammatory process of TBI. In addition, astrocyte apoptosis often occurs following the secondary injury of TBI. Yu et al³⁴ found that the

mouse lncRNA Gm4419 could promote the trauma-induced apoptosis of astrocytes by upregulating the expression of the inflammatory cytokine tumor necrosis factor- α (TNF- α). In particular, the lncRNA Gm4419 transcript could play the role of a sponge for miR-4661 (a miRNA that targets the 3' untranslated region of TNF- α for degradation and translation inhibition). However, the underlying mechanism by which lncRNA mediate the pathophysiological process of TBI requires confirmation by further research.

Ischemia generally proceeds after the occurrence of TBI.³⁵ Neurons cultured under an OGD condition are used as a common in vitro cell-damage model to simulate secondary pathophysiological changes after TBI.^{36,37} In the study by Yuan et al,³⁸ PC-12 cells were subjected to an OGD environment and then stimulated with geniposide, an iridoid glycoside that has been reported to exert a neuroprotective effect on these cells.³⁹ The treatment effect and the relative expression level of the lncRNA H19 were assessed. As a result, they found that geniposide protected PC-12 cells against OGD-induced injury via H19 upregulation. Human H19 has also been considered to alleviate hypoxia-induced injury by downregulating miR-28 expression in PC-12 cells.⁴⁰ Moreover, Yang et al⁴¹ found that the lncRNA SNHG1 protected against OGD-induced injury in brain microvascular endothelial cells by sponging miR-338. These studies give an insight into the role of lncRNA H19 and SNHG1 in ischemia and hypoxia injury after TBI. The different roles of lncRNAs in the pathophysiological process are summarized in Figure 1.

lncRNAs in the complication of traumatic brain injury

Traumatic optic neuropathy is one of the most feared and common complications of head and ocular trauma, for which a standard treatment has yet to be established.⁴² Yao et al.⁴³ investigated the role of MALAT1 in the retinal neurodegeneration of optic nerve transection models of rats and mice. They found that MALAT1 might modulate retinal neurodegeneration through binding to the cAMP response element-binding protein (CREB), maintaining CREB phosphorylation by inhibiting protein phosphatase 2 (PP2A)-mediated dephosphorylation, and thus resulting in continuous CREB signaling activation. In addition to cell apoptosis and inflammatory responses, oxidative stress also plays an important role in secondary injury after TBI.⁴⁴ Miao et al⁴⁵ explored the role of the lncRNA

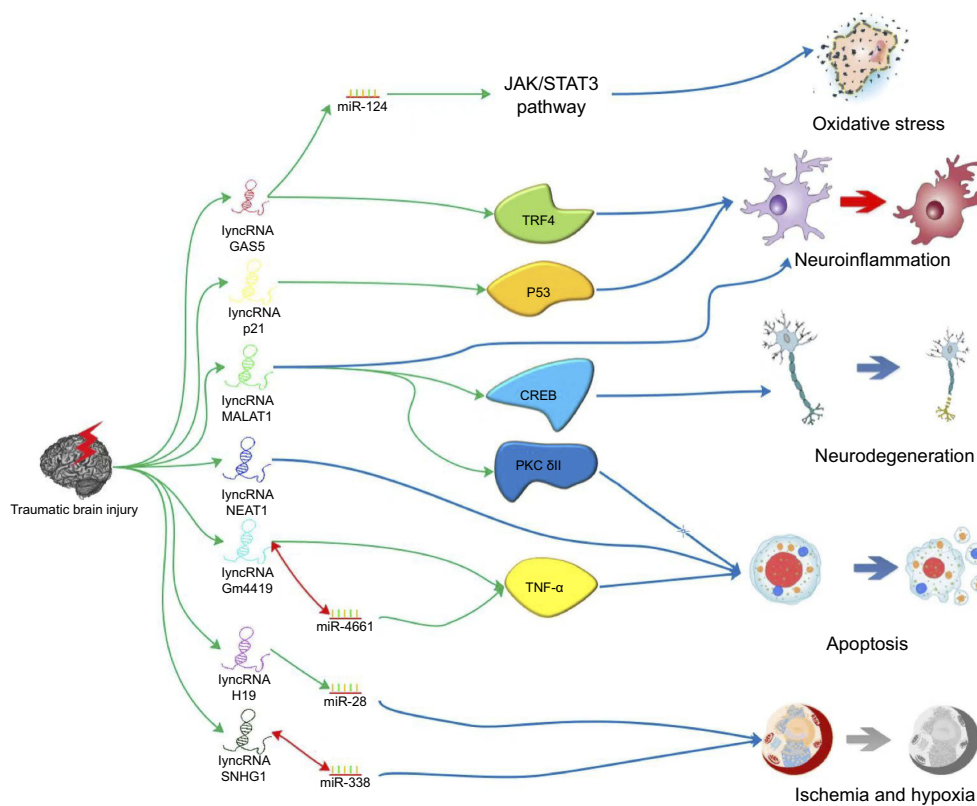


Figure 1 The probable mechanisms of the effects produced by lncRNAs on TBI.

Notes: There are several lncRNAs that have been reported to play different roles in the process of TBI. Knocking down GAS5 would alleviate RGCs oxidative stress injury by upregulating miR-124. GAS5 could also inhibit microglia M2 polarization by suppressing transcription of TRF4. lncRNA-p21 may promote microglial activation through a p53-dependent transcriptional pathway. In addition to neuroinflammation, lncRNA MALAT1 is also related to neurodegeneration and astrocyte apoptosis via CREB signaling pathway and alternative splicing of PKC δ II respectively. Astrocyte apoptosis are associated with NEAT1 and Gm4419 in which Gm4419 could play the role of sponge for miR-4661 which could target TNF- α . H19 is considered to alleviate hypoxia-induced injury by downregulated miR-28 expression. SNHG1 protected secondary cerebral ischemia and hypoxia via sponging miR-338.

Abbreviations: lncRNA, long noncoding RNA; TBI, traumatic brain injury; GAS5, growth arrest-specific 5; RGC, retinal ganglion cells; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; CREB, cAMP response element-binding protein; NEAT1, nuclear enriched abundant transcript 1; TNF- α , tumor necrosis factor-alpha; SNHG1, small nucleolar RNA host gene 1.

GAS5 in mice retinal ganglion cells (RGCs) that were subjected to H₂O₂ injury in order to simulate an in vitro oxidation stress model of optic nerve injury. They found that lncRNA GAS5 knockdown would elicited competing endogenous RNAs (ceRNA) activity by upregulating miR-124 to alleviate the RGC injury. This process might be associated with activation of JAK/STAT3 signaling pathway and inhibition of the JNK signaling pathway. The above studies identified the roles of lncRNA MALAT1 and GAS5 in retinal neurodegeneration and optic nerve regeneration, which could be potential mechanisms underlying traumatic optic neuropathy.

TBI and post-traumatic stress disorder (PTSD) commonly co-occur in TBI patients such as veteran populations or individuals exposed to severe trauma, causing similar symptoms like sleep, concentration, memory, and mood disorders.⁴⁶ PTSD and persistent sequelae due to TBI are thought to share common

pathophysiological elements related to the CNS after acute injury or threat.⁴⁷ PTSD affects a variety of physiological systems throughout the body, including the hypothalamus-pituitary-adrenal axis, cortical function, and immune system. Multiple biological studies on PTSD have been reported. As a novel research target, lncRNAs have also been explored with regard to their relationship with the PTSD model. Liu et al⁴⁸ established a rat model of PTSD-like syndrome and conducted a microarray analysis of the hippocampal tissues. For microarray analysis, an Agilent Array platform was employed (Agilent Technologies, Santa Clara, CA, USA). They showed 293 lncRNAs and 476 mRNAs to be differentially expressed. GO and pathway analyses indicated the association of these lncRNAs with multiple biological processes, cellular components and molecular functions. Among the abnormally expressed lncRNAs, lncRNA MPAK159688_P1 (associated with

the memory function-related *Fos* gene) was downregulated. Thus, lncRNAs would have promising value in discovering the mechanism of PTSD or sequelae due to TBI, and promoting effective rehabilitation.

lncRNAs in the treatment of traumatic brain injury

Inflammation commonly responds to TBI and leads to secondary brain edema, neuronal apoptosis, or cell death at different stages of the disease course. Patel et al¹⁰ isolated exosomes from human adipose-derived stem cells (hASCs) containing the lncRNA MALAT1, and then injected them intravenously into rats subjected to TBI. Exosomes depleted of MALAT1 or conditioned medium depleted of exosomes were also administered as control groups. They observed a significant recovery of motor function and amelioration of the cortical brain injury in the animals injected with the exosomes containing the lncRNA MALAT1. RNA-Seq suggested the MALAT1-dependent modulation of inflammation-related, cell cycle, and molecular regeneration pathways. The study demonstrated MALAT1 as a potential therapeutic approach for TBI. Similarly, MALAT1 from hASC exosomes was demonstrated to promote neuronal survival and cell proliferation after injury via alternative splicing of protein kinase C δ II in a mouse hippocampal cell line.⁴⁹ The upregulation of the lncRNA nuclear enriched abundant transcript 1 (NEAT1) has been shown to play a role in early apoptosis.⁵⁰ Bexarotene, a selective agonist of retinoid X receptor, could exert a neuroprotective effect against cell apoptosis after TBI.⁵¹ Zhong et al⁵² studied the association between lncRNA *Neat1* and bexarotene in the treatment of TBI in mice. They found that bexarotene promoted the level of NEAT1, which suppressed apoptosis and inflammation, thereby contributing to better motor and cognitive function recovery after TBI. Interestingly, Dai et al⁵³ investigated the effect of the traditional Chinese medicine Changqin No. 1 on TBI, and found that lncRNA GAS5 could upregulate RAS p21 GTPase activating protein 1 (*Rasa1*) expression via sponging miR-335 in mouse neuronal cells. Moreover, lncRNA GAS5 exerted a neuroprotective effect by inhibiting neuronal apoptosis, which exploited a new field that explains the therapeutic mechanisms of some traditional Chinese medicines.

Oligodendrocyte death following TBI can induce pathological changes in white matter, which commonly

results in network dysfunction and cognitive impairment.⁵⁴ As a distinguishing biomarker of developing oligodendroglia progenitors, A2B5 from induced pluripotent stem cells has the potential to ameliorate TBI by inducing differentiation of the iPSCs into oligodendrocytes.^{55,56} Lyu et al⁵⁷ performed a microarray analysis of lncRNAs and mRNAs in rats with TBI after A2B5-positive cell transplantation. The Agilent Array platform was employed for microarray analysis. They found 83 lncRNAs and 360 mRNAs to be differently expressed ($P < 0.05$, fold change > 2), with the crucial lncRNA and mRNA involved being ENSRNOT00000052577 and *Kif2c*, respectively. Therefore, the therapeutic effects of A2B5-positive iPSC transplantation could be related to the involvement of lncRNAs.

Future perspectives and conclusion

lncRNAs have received increasing attention for their ability to modulate transcriptional regulation in neurological diseases. The study on the roles of lncRNAs is currently at the infancy stage and their mechanisms remains to be elucidated. First, although alterations in lncRNA expression have been reported in TBI, more research focused on the multidimensional interactions of lncRNAs studies not limited to their function as ceRNAs, and comprehensive analysis of their expression profiles are needed. Second, alterations in the expression levels of lncRNAs in blood samples after TBI has not been studied to date. Such lncRNAs with abnormal findings upon blood test would have the potential to be novel biomarkers. Third, despite the existence of various in vitro models of primary injury in TBI, such as transection, compression methods, and stretch-induced injury,³⁵ most studies have only focused on cell models for secondary injury, such as the OGD and oxidative stress models. Therefore, in vitro experiments are relatively scarce and their validation function is not powerful enough.

In conclusion, lncRNAs have been recognized to play complex roles in TBI and may subsequently be promising biomarkers for diagnosis, evaluation, treatment, and prognosis prediction of this debilitating disease process. Future studies should focus on the detailed mechanisms and functional roles of lncRNAs so that targeted therapies for TBI can be developed.

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Disclosure

The authors report no conflicts of interest in this work.

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