A narrative review of long noncoding RNA: insight into neural ischemia/reperfusion mediated by two pathophysiological processes of injury and repair

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Background and Objective: A thorough understanding of the role of long noncoding RNAs (lncRNAs) in cerebral ischemia/reperfusion injury (IRI) is conducive to a comprehensive understanding of the molecular regulatory network of IRI. Such an understanding could be of great significance for finding new biomarkers and therapeutic targets of IRI. Such findings could protect important tissues and organs and improve the clinical prognosis of patients.

Methods: We conducted a literature search for published manuscripts on neural ischemia/reperfusion up to October 2021 in the PubMed, Web of Science, Cochrane Library, and EMBASE databases.

Key Content and Findings: LncRNAs are a group of regulatory sequences that play a role at the transcriptional, posttranscriptional and epigenetic levels. LncRNAs are highly expressed in the central nervous system and play an important regulatory role in the development of the central nervous system and diseases. The mechanism of IRI is complex, and pathological injury processes, such as apoptosis, oxidative stress injury, neuroinflammation, excitatory amino acid toxicity, autophagy and impaired blood–brain barrier function, are mutually intertwined or promoted. These processes can aggravate the secondary injury of brain tissue after ischemia–reperfusion. Moreover, cerebral IRI can induce a large number of changes to the expression of lncRNAs in the brain, suggesting that lncRNAs are related to the complicated pathological process of cerebral IRI.

Conclusions: In this narrative review, the roles of lncRNAs in cerebral IRI, apoptosis, anti-apoptosis, nerve regeneration, and repair after injury are reviewed. Additionally, possible future research directions for lncRNAs in ischemic stroke injury and repair are proposed.

Keywords: Long-chain noncoding RNA; cerebral ischemia/reperfusion injury; oxidative stress

Introduction

Ischemia reperfusion (IR) is a common pathological process that participates in a wide range of diseases, such as myocardial infarction, acute ischemic stroke, acute kidney injury, trauma, and circulatory failure. Restoring the blood supply to ischemic tissue in a timely manner is the best treatment strategy to improve the patient's condition. However, the recovery of the blood supply (1) also brings new damage to ischemic tissues and organs, namely, ischemia/reperfusion injury (IRI). Long noncoding RNAs (lncRNAs) has become a research hotspot in recent years.

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Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	Up to October 2021
Databases and other sources searched	PubMed, Web of Science, Cochrane Library, and EMBASE databases
Search terms used (including MeSH and free text search terms and filters) (Note: please use an independent supplement table to present detailed search strategy of one database as an example)	"neural ischemia/reperfusion", "injury", "repair", and "long noncoding RNA"
Timeframe	Up to October 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Qualitative and quantitative data were extracted by interpreting each paper in cycles to avoid missing potentially valuable data
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Qualitative and quantitative data were extracted by interpreting each paper in cycles to avoid missing potentially valuable data
Any additional considerations, if applicable	No

Many studies have proven that lncRNAs are involved in the pathological process of IRI in many important organs, such as the heart, brain, liver, kidney and vascular endothelium (2). Some lncRNAs have been proven to be biomarkers of IRI in brain tissue. In the future, lncRNAs may be a potential therapeutic target for preventing stroke IRI (3). Some lncRNAs have been proved to be biomarkers of IR. In the future, it may become a potential therapeutic target for the prevention of IR. Comprehensively exploring the biological function and molecular mechanism of lncRNAs is of great significance for us to study how to protect IRI of tissues and organs. It is of great significance for us to study how to protect tissues and organs from IRI by comprehensively exploring the biological functions and molecular mechanisms of lncRNAs. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-268/rc).

Methods

We conducted a literature search for published manuscripts on neural ischemia/reperfusion up to October 2021 in the PubMed, Web of Science, Cochrane Library, and EMBASE databases. We used the following search words and terms: "neural ischemia/reperfusion", "injury", "repair", and "long noncoding RNA". Qualitative and quantitative data were extracted by interpreting each paper in cycles to avoid missing potentially valuable data (*Table 1*).

Discussion

LncRNA

LncRNAs exist in the nucleus or cytoplasm of organisms. They do not encode proteins and are the transcription products of genes encoding very short polypeptides. At present, there is no unified view about the sources of lncRNAs (4). The recognized sources mainly include mutations of protein-coding genes, chromatin recombination, reverse transcription of noncoding genes, duplication of internal segments of noncoding RNA and insertion of transposable elements (5). RNA acts as a medium to regulate the internal conversion of pathways and signals. Four core nucleotides and a variety of chemically modified nucleotides regulate and stabilize the structure of RNA. LncRNAs are usually long, and they form poly A tails and promoter structures by splicing. Then, they form thermodynamically stable secondary or higher structures to perform their function after folding. Compared with coding RNAs, lncRNAs are more susceptible to species evolution, and their sequences are less conserved. More and more lncRNAs can be found in the genomes of organisms, and there are relatively conserved short sequences in their molecules, which are closely related to the important physiological and biochemical functions of expression (6). Therefore, lncRNAs have the characteristics of a specific secondary spatial structure, low sequence conservation but relatively conservative internal short sequences, developmental specificity, dynamic expression

during differentiation, and various shearing forms. RNA not only plays an auxiliary role as the intermediate carrier of genetic information but also plays a more important role in various regulatory functions (7). Similarly, lncRNAs have complex biological functions at the genetic and transcription levels. In recent years, it has been found that the functions of lncRNAs at the molecular level mainly include three aspects. First, chromatin modifying proteins are collected to regulate gene expression (8). It has been found that the inactivation-specific transcript of the X chromosome transcribed from the X chromosome can recruit multicomb suppression complex 2. This can inhibit gene transcription on the X chromosome, inactivate the genetic traits of one X chromosome in mammalian females, and achieve the goal of maintaining the same gene phenotype of male and female organisms (9). In addition, lncRNAs related to chromosome modifications other than the X chromosome are being continuously identified, and such lncRNAs include the Kcnq1 antisense transcript and Igf2 antisense transcript. Second, when combining with DNA or some RNA through base complementation lncRNAs play a regulatory role at the transcriptional and posttranscriptional levels by modifying the promoter structure, changing the cleavage site and covering the binding site. For example, an Alu sequence lncRNA regulates the transcription process by combining with RNA polymerase II to achieve the goal of gene suppression (10). Third, lncRNAs directly affect the function of proteins by changing their location in the cytoplasm, combining with specific proteins and forming nucleic acid-protein complexes. For example, lncRNA ADORA2A was found to exerts tumor-suppressive roles via binding the RNA stable protein Hu antigen R and repressing Fascin Actin-Bundling Protein 1 (11).

LncRNA and IR

The brain is the most sensitive organ to the ischemic response. Cerebral ischemia will cause irreversible damage to brain tissue in less than 20 min. IR-induced brain microvascular endothelial cell injury is the initial stage of blood–brain barrier injury, which leads to poor prognosis in patients with ischemic stroke (12). Studies have proven that autophagy has a protective effect on ischemic injury in brain microvascular endothelial cells. Li *et al.* (13) found that the level of metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) in brain microvascular endothelial cells was significantly increased

in an IR mouse model. Furthermore, the expression of ULK2 was downregulated by inhibiting the level of miR-26b, which promoted autophagy and cell survival of brain microvascular endothelial cells. Wang *et al.* (14) found that MALAT1 expression increased PI3K activity and AKT phosphorylation but decreased Caspase-3 activity in an IR model of brain microvascular endothelial cells. It also inhibited the apoptosis of brain microvascular endothelial cells. Zhang *et al.* (15) found that the level of MALAT1 was significantly increased after IR in mouse models of both brain microvascular endothelial cell IR and brain IR. Studies have shown that MALAT1 can inhibit apoptosis by inhibiting the levels of the proapoptotic factor BIM and the proinflammatory factors MCP-1, IL-6 and endothelial cell selectin, thus protecting against IRI in cerebral apoplexy. Extensive studies have shown that IRI not only causes brain microvascular endothelial damage but also triggers a series of neural events, such as hypoxia, oxidative stress, neurotoxicity, inflammatory reaction and edema formation, leading to the death of neurons in ischemic areas (16). Wu *et al.* (17) detected the change in the expression profile of whole genome lncRNAs in a mouse model of brain IRI and found that lncRNA-N1LR may inhibit apoptosis by inhibiting phosphorylation of the 15th serine residue of the p53 protein, thus protecting nerve cells. Li *et al.* (18) also screened lncRNAs after IRI in mouse hippocampal neurons with high throughput and found that lncRNA-Tnxa-psi promoted the survival of neurons by inhibiting apoptosis.

Mechanisms of noncoding RNAs in the IR process

Cell damage and death

Reperfusion injury after cerebral ischemia refers to brain cell damage in the ischemic area that continues to worsen after blood flow is restored. Cerebral ischemia is the first disabling factor, and reperfusion injury after cerebral ischemia is harmful. Therefore, effective control of reperfusion injury is of great benefit to patients with cerebral ischemia. Thai *et al.* (19) found that the endotoxins in damaged cells were significantly increased and the cell survival rate was significantly decreased after the knockout of a lncRNA named SCAL1, which indicates that SCAL1 plays an important role in cell survival. The NF-κB pathway is a cellular and molecular pathway closely related to IRI. Activation of the NF-κB pathway can aggravate the loss of integrity of the blood–brain barrier when injury occurs (20).

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After the blood barrier is destroyed, many inflammatory factors further aggravate cell damage through blood vessels with increased permeability. Additionally, the expression of specific lncRNAs in vascular endothelial cells is increased, which regulates cell damage. The extra-domain A (EDA) is an extra domain of alternative splicing exons encoding type III repeats, and it is closely related to the tissue injury response. Studies have shown that some lncRNAs are related to EDA production (21,22). Apoptosis is an active process under the action of a series of gene activation, expression and regulation. After cerebral ischemia, injured and necrotic cells are mainly located in the ischemic central area, while apoptotic cells are located in the peripheral areas. Apoptosis of brain cells is not necrosis. Many neurons in the ischemic penumbra or infarct area have the potential to recover after a period of ischemia (23). Inhibition of apoptosis is of great help to the prognosis of stroke patients. It has been reported that Zusanli electroacupuncture can inhibit apoptosis and help to improve cerebral ischemia (24). P53 is a tumor suppressor gene, and its encoded protein is a transcription factor that controls the start of the cell cycle. When the cell is damaged and cannot be repaired, the p53 protein participates in the start-up process and causes damaged cells to die via apoptosis (25). The expression of p53 is rapidly increased in ischemic stroke. Recent studies have shown that lncRNA-ROR negatively regulates the expression of p53 by inhibiting the binding of hnRNPI to p53 mRNA, which is induced by stress. These findings suggest that lncRNA-ROR indirectly regulates apoptosis after cerebral ischemia. Zhou *et al.* (26) that lincRNA-p21 can directly bind to the MDM2 protein and inhibit the binding of P53 and MDM2, thus affecting the function of p53 (*Figure 1*).

Excitotoxicity

Excitotoxicity is one of the important mechanisms of ischemic brain injury. Under conditions of anoxia and glucose deficiency, the energy metabolism of cells is obstructed. Such obstructions can lead to a decrease in ATP-dependent sodium and potassium pump activity, a significant increase in extracellular K^+, membrane depolarization, a large release of excitatory amino acids, excessive excitation of postsynaptic neurons, the activation of ionic glutamate receptors on cell membranes, the promotion of extracellular Ca^{2+} influx, the aggravation of intracellular calcium overload, and a series of events, such as cell swelling, necrosis and apoptosis (26). Ionic glutamate

receptors can be divided into NMDA receptors and AMPA receptors (27). The AMPA family includes GluR1-44 subunits, among which the GluR2 subunit can regulate the permeability of the AMDA receptor to Ca^{2+}. However, REST can facilitate gene expression by upregulating the activity of the gene promoter of the GluR EAAT2, which affects Ca^{2+} influx after excitotoxicity brain injury (28,29). Recently, it has been found that under the induction of stroke, more lncRNA binds to the REST coinhibitors Sin3A and coREST and regulates REST-mediated gene silencing at the epigenetic level (30).

Oxidative

Nerve cells and endothelial cells produce a large amount of reactive oxygen species (ROS) during mitochondrial respiratory chain injury and reperfusion after ischemia. ROS can damage proteins and DNA and transmit cell necrosis and apoptosis signals (31). ROS can directly activate the mitochondrial permeability transition pore (MPTP) on the mitochondrial membrane or induce p53 to bind to cyclophilin D to open the MPTP. This binding can lead to mitochondrial swelling and further blockage of the mitochondrial respiratory chain and ultimately promotes cell necrosis in the ischemic core area (32). In addition, ROS can activate p38MAPK and mediate the apoptosis of ischemic penumbra cells through the caspase pathway. The pathological process of ischemic stroke can activate two antioxidant pathways: the superoxide dismutase pathway and the Nrf2/ARE pathway (33,34). Signal transduction and activator of transcription 3 (STAT3) is inactivated during reperfusion injury, which leads to a decrease in SOD2 gene expression regulated by STAT3. Bioinformatics methods predict that 120 lncRNAs contain STAT3 binding sites, which suggests that lncRNAs may regulate the expression of SOD genes through STAT3 (35). Under physiological conditions, Keap1 binds to Nrf2, inhibiting its biological activity (36). Under oxidative stress, ROS promote its separation. Then, free Nrf2 binds to the ARE, which induces the expression of antioxidant proteins. Recent studies have shown that SCAL1, a newly discovered lncRNA, increases SCAL1 expression in the endothelial cells of patients with lung cancer caused by smoking. SCAL1 is the downstream molecule of Nrf2. SCAL1 knockout leads to an increase in endotoxins and a decrease in the cell survival rate, which means that SCAL1 plays an important role in the Nrf2/ARE antioxidant pathway (19) (*Figure 2*).
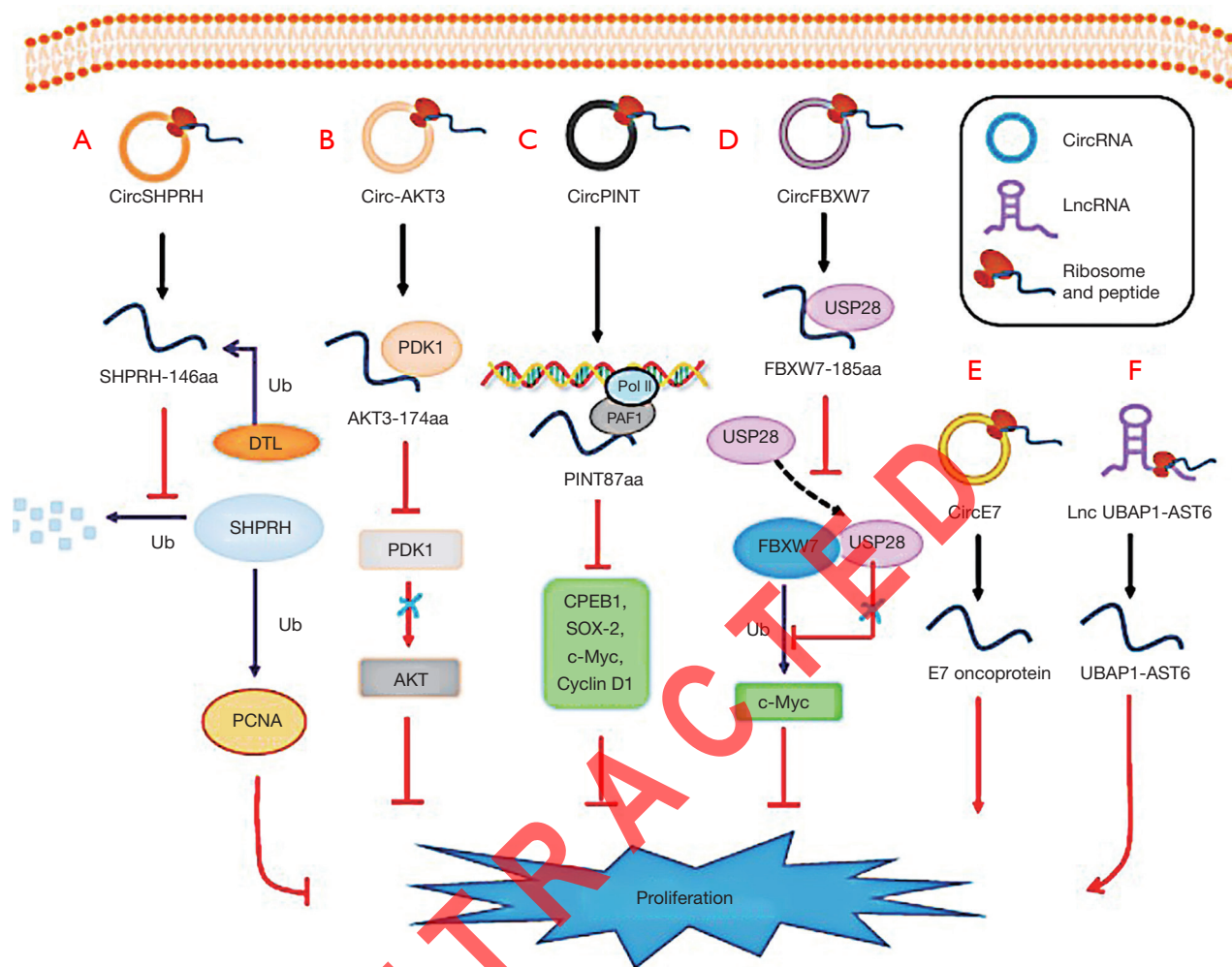
Figure 1 Mechanism of lncRNAs in ischemia–reperfusion injury. SHPRH, SNF2 histone linker PHD RING helicase; AKT3, AKT serine/threonine kinase 3; FBXW7, F-box and WD repeat domain containing 7; PDK1, pyruvate dehydrogenase kinase 1; DTL, denticleless E3 ubiquitin protein ligase homolog; PCNA, proliferating cell nuclear antigen; USP28, ubiquitin specific peptidase 28.

Inflammatory

Ischemic stroke rapidly leads to early local inflammatory reactions, including microglial activation and cytokine secretion. With the extension of time, the infiltration of consanguineous macrophages and lymphocytes is also involved in the pathological process of ischemic stroke (37). In the brain, TLR is mainly expressed on the surface of microglia, astrocytes and oligodendrocytes and plays a regulatory role in the activation of the inflammatory response and the secretion of cytokines after cerebral ischemia. Activation of TLR2 after cerebral IRI can cause microglia to secrete IL-23, IL-17 and other cytokines that can damage neurons (38). The expression level of TLR4

was increased after cerebral ischemia, and TLR4 could regulate the expression of TNF-α, COX-2, iNOS and other cytokines (39). The signal transduction of TLR2 and TLR4 mainly depends on the MyD88-dependent pathway and MyD88-independent pathway, and it eventually leads to the activation of NF-κB and the production and secretion of cytokines. Chen *et al.* (40) found that inhibition of lncRNAAK139328 can significantly decrease the level of Akt in liver IRI. Additionally, Akt binds to NF-κB, which inhibits its nuclear metastasis and reduces the expression of inflammatory factors. Wang *et al.* (41) also found that ROCK2, which can promote the inflammatory response after cerebral IRI, has a certain relationship with lncRNAs. Covarrubias *et al.* (42) found that TLR-induced
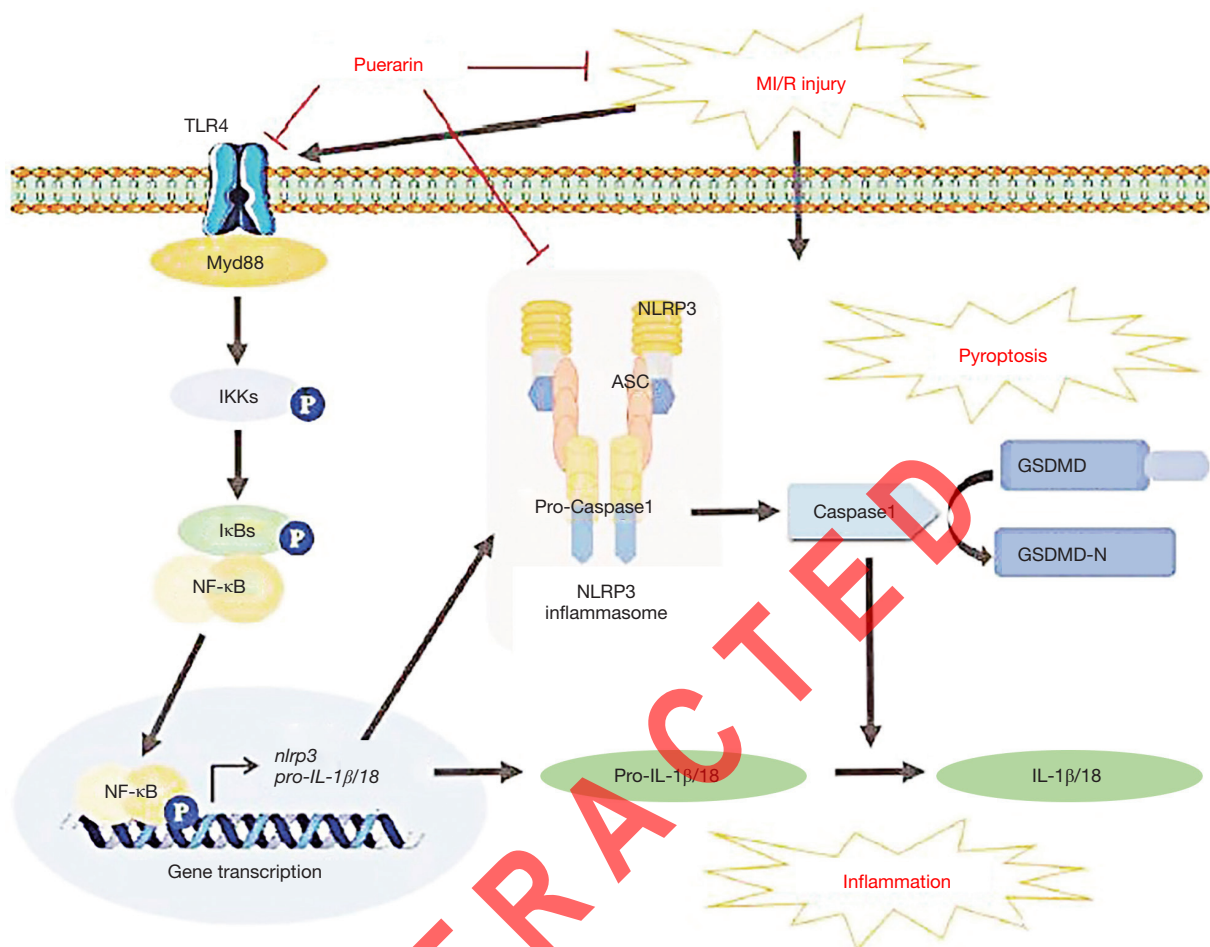
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Figure 2 Mechanism of inflammation in ischemia–reperfusion injury. MYD88, MYD88 innate immune signal transduction adaptor; TLR4, toll like receptor 4; NLRP3, NLR family pyrin domain containing 3; GSDMD, gasdermin D.

macrophage lincRNA-Cox2, enhanced the expression of IL-6, and bidirectionally regulated the inflammatory reaction by binding to hnRNPs. All these results indicate that lncRNAs play an important role in the inflammatory response after cerebral IRI.

Destruction of blood barrier

Cerebral vascular endothelial cells are an important part of the blood–brain barrier (43). Damage to endothelial cells after cerebral ischemia can lead to destruction and dysfunction of the blood–brain barrier, changes in the permeability and integrity of cerebral vessels, vasogenic brain edema, the production of inflammatory factors or the promotion of a large number of inflammatory factors in the ischemic injury area. Such conditions aggravate cell necrosis and

apoptosis (44). In cerebrovascular endothelial cells, there is some specific expression of ncRNAs, such as miR-101, miR-125a, miR-155, linc00439, Meg3, MALAT1, and TUG1 (45,46). However, little research has been done on their role in injury and protection of the vascular endothelium after stroke (45). Although some miRNAs have been reported to regulate the apoptosis of vascular endothelial cells after stroke and its protective mechanism, the newly discovered role of lncRNAs in vascular endothelial cells after ischemic stroke is still rarely reported (47). This role could provide a new direction for pathological research and the treatment of ischemic stroke in the future.

Role of lncRNA in nerve repair after IR

For a long time, the central nervous system has not been

considered to have the function of regeneration after injury. Recently, however, it has been found that there are endogenous neural stem cells (NPCs) in the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus of the hippocampus (48). After cerebral ischemia, these neural stem cells begin to differentiate into neurons and glial cells and gradually migrate to ischemic injury areas. This means that nerve repair will become another important treatment measure for ischemic stroke after nerve protection (49). Nerve repair after stroke mainly includes nerve regeneration, blood vessel regeneration, oligodendrocyte regeneration and astrocyte regeneration, which together determine the functional integrity of nerve and blood vessel units after injury (50). Nerve regeneration promotes nerve plasticity and functional recovery. Oligodendrocyte regeneration repairs neuron signal transduction and promotes myelination. Vascular regeneration increases blood flow in the ischemic area and regulates nerve regeneration and glial cell regeneration (51).

Angiogenesis

Vascular endothelial cells (VECs) are single-layer flat cells lining the lumen of blood vessels, and their activation, proliferation and migration are essential intermediate processes of angiogenesis. Xiong and others (45,46) found that endothelial cells were damaged after cerebral ischemia. They also found that the expression of specific lncRNAs that are highly expressed in vascular endothelial cells, such as linc00493, Meg3, and MALAT1, is increased, which might be related to the injury and repair of endothelial cells (52). Moreover, it was found that the cell cycle of vascular basal endothelial cells was inhibited, the number of basal cells decreased, and cells migrated and germinated to block new blood vessels after MALAT1 was knocked-out in mice. These findings suggest that MALAT1 is involved in regulating angiogenesis. Vascular endothelial growth factor (VEGF) can promote the proliferation of vascular endothelial cells (52,53). Its synthesis level is very low in normal tissues of animals and adults, but it is high in embryos and tissues with angiogenesis. VEGF is considered to promote capillary fusion in angiogenesis. There are multiple types of VEGF, including VEGF-A, -B, -C, -D and -E types. Among these types, VEGF-A can promote the mitosis of endothelial cells and increase the permeability of vascular endothelial cells (54). The VEGF receptors R-1, R-2 and R-3 are distributed on the surface of vascular endothelial cells (55). Huang *et al*. (56) found that maternal

transcript 3 (Meg3) of noncoding RNA can significantly affect the expression of VEGF-A and VEGFR-1, which indicates that Meg3 is closely related to angiogenesis. Nitric oxide (NO) is an important messenger molecule and cell growth regulator related to blood vessels. Nitric oxide synthase (NOS) is the rate-limiting factor of NO production (57). NOS is usually used to locate the distribution of NO. Endothelial nitric oxide synthase (eNOS) is type of a NOS in endothelial cells. Ling and others have clarified the mechanism of NO and eNOS in endothelial cells (58). Xu *et al*. (59) reported that the long noncoding RNA AK094457 plays a role in regulating blood vessels by influencing the production of eNOS. Further research has clarified the mechanism by which the multiprotein complex bound by the eNOS3'UTR can stabilize eNOS mRNA and further interfere with its transcription process to regulate angiogenesis (60).

LncRNA and nerve repair

Recent research has shown that after the central nervous system is injured by ischemia, the body will trigger a series of reactions to promote the recovery of injured nerves. Jin *et al*. explained the neuroprotective process of autophagy that occurs in organisms (61). An and others (62) found that after ischemia, some endogenous neural stem cells (NPCs) migrate to the ischemic area and gradually differentiate into neurons and glial cells. Studies have found that more than 30 kinds of lncRNAs are highly expressed in mature neurons. Among these is lncRNAN1, which is involved in regulating gene expression and NPC differentiation. lncRNAN2 can indirectly mediate the occurrence of nerve cells, and the expression of the transcription factor SOX2 can promote NPC differentiation into nerve cells. Some studies have found that lncRNA RMST can bind to the promoter region of the SOX2 target gene and influence the differentiation direction of NPC (63). Recent studies have shown that lncRNAs can also regulate the regeneration and differentiation of neurons by regulating target proteins in the process of nerve regeneration. Glial cells are widely distributed in the central and peripheral nervous systems, and they support and guide the migration of neurons (64). They are divided into astrocytes, oligodendrocytes and microglia, which participate in the repair and regeneration of the nervous system. The main functions of oligodendrocytes are to surround axons, form myelin sheath structures and assist in the transmission of nerve electrical signals. Thus, they maintain and protect

the normal function of neurons. Studies that analyzed the expression profiles of lncRNAs and mRNAs in injured rat sciatic nerves found 105 lncRNAs that were differentially expressed. They also found that the migration of glial cells was affected, which indicates that lncRNAs could regulate the migration of glial cells (65). In addition, after decreasing the expression level of lncRNA BC089918 in cells, the axons of nerve cells were elongated, which indicates that lncRNAs can inhibit nerve regeneration.

Conclusions

In summary, lncRNAs are widely involved in various regulatory pathways, such as apoptosis, autophagy, necrosis, and inflammatory reactions, in the process of cerebral ischemia-reperfusion and play an important role. The structure and function of lncRNAs are highly diverse, and lncRNAs play an important role in many human diseases. As a biological marker and therapeutic target, lncRNAs have been widely studied and applied in the field of oncology, but research on lncRNAs in IR is still in its infancy. The specific working mechanism of many lncRNAs is still unknown. In particular, the role of lncRNAs in IRI of lung tissue is unknown, and more research is required to further explore this topic. With the rapid development of science and technology, high-throughput sequencing provides a very convenient method for lncRNA research. There are an increasing number of studies using gene chip technology to discover known and unknown lncRNAs that are differentially expressed in IRI and to further explore their functions. The popularization of this technology is also an inevitable trend for studying lncRNAs in the future. Understanding the functions and mechanisms of these lncRNAs is expected to clarify their complex regulatory mechanisms in IRI.

Acknowledgments

Footnote

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