A review of the relationship between long noncoding RNA and post-stroke injury repair

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Abstract
Stroke is a cerebrovascular circulation disorder with sudden onset, which causes disorder of ion balance, inflammation, and acidosis, and that in turn induces ischemia-reperfusion injury, influencing the prognosis of stroke patients. Long noncoding RNAs (lncRNAs) are regulatory sequences involved at the transcriptional, post-transcriptional, and epigenetic levels, have high specific expression in the central nervous system, and effectively regulate the development of the central nervous system and progression of diseases. Stroke induces changes in the expression of many lncRNAs. Therefore, lncRNAs play an important role in the complex pathological process of stroke. Exploring lncRNA could facilitate a comprehensive understanding of the pathological mechanism of stroke and the post-injury molecular regulatory network. However, there are few reports on the role of lncRNA in the pathological development of stroke. In the present review, we discuss the association of lncRNA with post-stroke injury repair.

Keywords
Stroke, lncRNA, injury repair, cerebrovascular disease, revascularization, nerve repair

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Introduction

Stroke is an acute cerebrovascular disease induced by damage to brain tissue arising from the sudden rupture of blood vessels in the brain or the obstruction of blood vessels, which inhibits blood flow into the brain. At present, stroke is clinically divided into two main types: hemorrhagic stroke and ischemic stroke. Ischemic stroke is the most common, accounting for approximately 60% to 70% of the total incidence. Once a stroke occurs, irreversible damage will occur, within a very short time, in the core site of the ischemic focus. Then, it extends towards the ischemic penumbra as the disease progresses, and secondary nerve apoptosis is induced through the comprehensive effects of inflammation, cell apoptosis, and immune response, leading to post-stroke transcription factor disorder, and induction of ischemic penumbra neurological deficit. Therefore, in protecting post-stroke brain tissues and restoring nervous function, the mechanism of stroke injury and the regeneration of nerves and blood vessels after injury are particularly important.

Long noncoding (lnc)RNA is a transcript of RNA with a length > 200 nucleotides but without an open reading framework. It is mostly found in the nucleus, is transcribed through RNA polymerase II or RNA polymerase III, and has strong space-time and tissue specificity. Therefore, it has an important regulatory effect in the phylogenetic process. In addition, lncRNA plays an important role in epigenetic regulation, cell cycle regulation, and cell differentiation regulation. The main mechanisms of lncRNA are as follows. (1) As a scaffold, lncRNA binds to domains through different effector molecules to provide a place for the assembly of regulating complexes. (2) It forms a specific spatial structure and play a guiding role in RNA binding to specific regulatory site proteins. (3) Its biological function is fully exerted by recruiting other molecules. For example, it effectively regulates the target gene expression of microRNAs (miRNAs) by adsorbing specific miRNAs. (4) As a signaling molecule, it transmits the regulatory signals of biological development through its spatiotemporal expression specificity and subsequently plays a regulatory role in the expression of related genes.

LncRNA is closely correlated with the development and function of the central nervous system. Its expression in the human body is tissue-specific, and it has different expression profiles and abundances in different tissues. Research has revealed that the expression of noncoding RNA (ncRNA), including lncRNA and miRNA, changes significantly in the brain of stroke patients. Therefore, understanding the role of lncRNA in the pathological process of stroke is particularly important. Exploring lncRNA could help to elucidate the pathological mechanism of stroke and the post-injury molecular regulatory network. However, there are few reports on its role in the pathological development of stroke. In the present review, we discuss the associations between lncRNA and post-stroke injury repair.

The role of lncRNA in nerve repair after brain injury

Endogenous neural progenitor cells (NPCs) are widely distributed in the subventricular zone (SVZ) and subgranular layer of the dentate gyrus of the hippocampus. These cells differentiate into neurons and glial cells after cerebral ischemia and gradually migrate to the injured area. Therefore, nerve repair is an effective measure for the treatment of stroke. Nerve and vascular regeneration, astrocyte regeneration, and oligodendrocyte regeneration are the main components of post-stroke nerve repair, which plays an important role in ensuring...
the integrity of neurovascular unit function after injury.\textsuperscript{12,13}

**The role of lncRNA in neural differentiation**

After cerebral ischemia, the number of NPCs in the SVZ significantly increases through a shortening of the NPC cell cycle. Then, NPCs migrate to the injured area and gradually differentiate into mature neurons.\textsuperscript{14,15} Thirty-five lncRNA, including lncRNA-N1, lncRNA-N3, and lncRNA-N2, are highly expressed in mature neurons, and lncRNA-N1 interacts with REST/coREST (RE1-silencing transcription factor/C-terminal cofactor for REST) in regulating gene expression and NPC differentiation. The association between lncRNA-N3 and SUZ12 plays a role in gene epigenetic silencing. LncRNA-N2 regulates the expression levels of miR-125b and Let-7a in NPCs and plays a role in mediating the regeneration of nerve cells.\textsuperscript{16,17} Furthermore, the expression of transcription factor SOX2 promotes the differentiation of NPC into neurons, while lncRNA RMST regulates the direction of NPC differentiation by binding to the promoter region of the SOX target gene. The expression of AK044422 significantly increases in \(\gamma\)-aminobutyric acid (GABA) neurons but is downregulated in oligodendrocytes. In addition, AK044422 is located in the genome and overlaps with miR124a, which promotes neurodifferentiation and specific expression in the brain. Therefore, AK044422 can be used as an important node molecule in the co-regulation network of miRNAs and lncRNAs.\textsuperscript{18–20}

**The role of lncRNA in oligodendrocyte regeneration**

The myelin sheath produced by oligodendrocytes during the progression of stroke envelops the axon surface to protect neurological function.\textsuperscript{21} The P13K/Akt and Wnt signaling pathways promote oligodendrocyte differentiation.\textsuperscript{22} Shh increases the production of helix-loop-helix (HLH) transcription factor Olig2 by inducing nerve cells, effectively regulating oligodendrocyte production.\textsuperscript{23–25} In addition, SOX8 complementary chain coding lncRNA SOXOT regulates oligodendrocyte maturation by sharing a promoter with SOX8, promoting oligodendrocyte regeneration.\textsuperscript{26,27}

**The role of lncRNA in vascular regeneration**

The cerebral ischemia penumbra region induces a vigorous vascular regeneration and contribute to nerve regeneration. However, the neocapillary density will have a serious effect on the prognosis of stroke patients.\textsuperscript{28,29} Vascular endothelial cell proliferation and differentiation play an important role in vascular regeneration, whereas the Notch signal regulates the migration of endothelial cells and stabilization of new blood vessels. Furthermore, vascular endothelial growth factor (VEGF) signal regulates the proliferation and differentiation of endothelial cells in vascular regeneration. Therefore, the Notch and VEGF signals play an important role in the process of vascular regeneration.\textsuperscript{30–32} In the development of stroke, loss of Meg-3 increases gene expression in the Notch and VEGF pathways and promotes an increase in cerebrovascular density. Previous studies have revealed that there are numerous highly expressed lncRNAs in vascular endothelial cells. Among these, linc00657, TUG1, Meg03, MALAT1, and linc00439 are conserved in both humans and mice.\textsuperscript{33–35} MALAT1 inhibits the cell cycle of basal endothelial cells, promote cell migration and germination, and, in turn, obstruct new blood vessels. However, the mechanism of MALAT1 in regulating the cell cycle is not fully
understood and needs further research.36–38 In addition, Tie-1 binds to the Tie-1 region to encode lncRNA tie-1AS, resulting in disruption of endothelial cell contact at a later stage and the effective inhibition of intercellular pipelines produced by the stimulation of VEGF, causing loss of cellular mucosal function and effectively avoiding vigorous vascular regeneration.39,40

**The role of lncRNA in neuroinflammation**

Astrocytes are the most abundant glial cell type in the central nervous system. Astrocytes have been a primary focus of researchers in neuropathology and neurophysiology, and they play an essential role in provision of energy metabolites to neurons and maintenance of the extracellular balance of ions. Recent studies have begun to examine the effects of lncRNAs on astrocyte proliferation and reactive gliosis. A previous study showed that lncRNA Gm4419 could promote trauma-induced astrocyte apoptosis by upregulating the expression of the inflammatory cytokine tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and the upregulation of TNF-\(\alpha\) was possible via competitively binding miR-466 1 49. Therefore, identifying the crucial lncRNAs to regulate astrocyte proliferation and activation has become the main concern in treating stroke.

**Summary and prospects**

LncRNA plays a regulatory role in the physiological and pathological processes of various diseases. Furthermore, its regulation mechanism is complex, its sequence is long, and it is highly conserved. Hence, it regulates physiological processes at different levels. In the development of stroke, several lncRNAs are specifically expressed in the central nervous system. A better understanding of the regulatory mechanism of lncRNA may lead to more comprehensive and complete treatment plans and provide a basis for omnidirectional molecular targeted therapy.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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