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*Review Article*

# Pathophysiology of Ischemic Stroke: Noncoding RNA Role in Oxidative Stress

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Stroke is a neurological disease that causes significant disability and death worldwide. Ischemic stroke accounts for 75% of all strokes. The pathophysiological processes underlying ischemic stroke include oxidative stress, the toxicity of excitatory amino acids, ion disorder, enhanced apoptosis, and inflammation. Noncoding RNAs (ncRNAs) may have a vital role in regulating the pathophysiological processes of ischemic stroke, as confirmed by the altered expression of ncRNAs in blood samples from acute ischemic stroke patients, animal models, and oxygen-glucose-deprived (OGD) cell models. Due to specific changes in expression, ncRNAs can potentially be biomarkers for the diagnosis, treatment, and prognosis of ischemic stroke. As an important brain cell component, glial cells mediate the occurrence and progression of oxidative stress after ischemic stroke, and ncRNAs are an irreplaceable part of this mechanism. This review highlights the impact of ncRNAs in the oxidative stress process of ischemic stroke. It focuses on specific ncRNAs that underlie the pathophysiology of ischemic stroke and have potential as diagnostic biomarkers and therapeutic targets.

## 1. Introduction

Globally, stroke is the cause of the second-highest deaths and the most disability-adjusted life years (DALYs). Stroke is a significant economic burden and stress on society worldwide [1, 2]. Nearly 60% of all strokes occur in people under 70 years old, and stroke incidence rates have shown a sharp and steady increase among young people aged 15 to 49 years [3]. Strokes can be classified into hemorrhagic or ischemic strokes, and the latter accounts for nearly 87% of all stroke cases [4]. A cerebral artery embolism leads to ischemic stroke with ischemia and hypoxia in the infraction of the corresponding brain areas, resulting in neuronal death and irreversible neurological deficits. After ischemia, neurons can immediately not maintain their normal transmembrane ion gradient and homeostasis. This triggers several processes that lead to cell death, such as excitotoxicity, oxidative and nitratative stress, inflammation, and apoptosis. These pathophysiological processes are highly detrimental to neurons, glial, and endothelial cells [5–7]. They are interrelated and continuously trigger each other in a positive feedback loop that destroys neurons [8]. Furthermore, ischemia-reperfusion injury (IRI) that occurs once blood flow is restored may exacerbate these processes [9]. During rapid blood flow recanalization, the demand for sugars and oxygen

increases rapidly, oxidase is activated in large amounts, and the degree of tissue oxidation increases greatly. These changes result in a cellular "oxidative burst" and excessive formation of reactive oxygen species (ROS), leading to secondary cerebral ischemia and reperfusion brain damage. As the most basic and critical pathological progression of brain injury, oxidative stress causes neuronal apoptosis, activation of inflammatory signaling pathways, and impairment of the blood-brain barrier (BBB) [10–12].

ncRNAs are a class of functional RNAs. While they cannot code for proteins, ncRNAs regulate gene expression in a posttranscriptional manner, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) [13, 14]. NcRNAs have been reported to be abundantly expressed in the mammalian brain. Additionally, recent studies have depicted that cerebral ischemia alters the expression profiles of ncRNAs [15, 16]. According to many studies, ncRNAs are involved in oxidative stress by controlling transcription and translation, thereby affecting neuronal cell survival [17–19].

Despite the unfavorable results of clinical trials, preclinical studies have suggested that oxidative stress damage may be a potential therapeutic target in ischemic stroke. Dysregulation of ncRNAs is a known mechanism contributing to cerebral ischemia, and potential biomarkers and therapeutic targets for treating cerebral ischemia have been identified. However, none of these breakthroughs have been successfully implemented in clinical practice. This review is aimed at discussing the role of noncoding RNA in oxidative stress in postischemic stroke brain injuries to lay the foundation for therapy and prophylaxis.

## 2. Oxidative Stress in Ischemic Stroke and Ischemia-Reperfusion Injury

The brain accounts for 20% of the total oxygen consumption. Accordingly, it has poor tolerance to hypoxia. When blood flow is interrupted, the ischemic area of the brain cannot maintain redox homeostasis and ion balance due to the lack of oxygen and glucose, which affects cell electrochemistry, metabolism, and the release of toxic products. Anoxic depolarization and various processes are triggered by the massive efflux of $K^+$ and influx of $Na^+$, water, and $Ca^{2+}$. These result in oxidative and nitrosative stress, excitotoxicity, inflammation, and apoptosis, eventually injuring neurons, glia, and endothelial cells [5, 7, 20–22]. During this process, numerous free radicals are formed, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), which participate in the breakdown of antioxidant systems and lead to brain damage caused by ischemic stroke as well as cerebral ischemia-reperfusion injury [23]. However, two phases of ischemia and reperfusion have differences with regard to the source of free radicals and state of oxidative stress.

*2.1. Oxidative Stress in the Phases of Ischemia.* During the ischemic period, restricted oxygen availability is associated with acidosis, energy deficiency, and changes in ion homeostasis, leading to compensatory brain dysfunction and eventually neuronal death [24, 25]. In the presence of residual oxygen, e.g., in low-flow ischemia, ROS is produced mainly in mitochondria. Under physiological conditions, superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase, and other antioxidant enzymes can aid in maintaining a neutral balance and catalytically protect brain tissues from the cytotoxicity of reactive oxygen species [26]. In addition, ROS play a physiological role by regulating immune system function, maintaining redox homeostasis, and participating in various metabolic pathways, even as second messengers [27, 28]. Endothelial cells rich in mitochondria are efficient sources of ROS. Due to their inherent characteristics and environmental factors, they are especially vulnerable to oxidative stress-induced damage. The effects of ROS include excessive lipid peroxidation and alterations in the functions of receptors, ion channels, and other membrane proteins, subsequently affecting the fluidity and permeability of cell membranes [29–31]. These pathologies cause damage to the blood-brain barrier (BBB) and often lead to leukocyte infiltration and edema [32, 33]. Furthermore, neuronal function relies on the continuous availability of ATP. As ischemic stroke depletes oxygen in the brain, neurons can no longer maintain their transmembrane gradient, and neuronal signaling is impaired [34]. In addition, glucose and oxygen deprivation inhibits ATP synthesis and blocks Na/K-ATPase activity. As a result, calcium ions flow into the cell [29–31]. Increased $Ca^{2+}$ concentration activates cyclases (cox-1 and cox-2) and phospholipase A2, which not only increases ROS production but also enhances glutaminergic neurotransmission [32, 35]. Increased levels of sodium, calcium, and adenosine diphosphate (ADP) also contribute to the overproduction of mitochondrial ROS (mROS) [36, 37]. inducing neuron apoptosis and death [38, 39].

Nitric oxide (NO) is another substance that promotes oxidative stress. NO peaks rapidly at 0.5 h after MCAO and immediately decreases to a low level at 4 h together with eNOS/Nnos. Then, NO gradually increased with the increase in iNOS and peaked at 46 h [40]. In studies of ischemic stroke patients, increases in NO metabolites from day 1 to day 2 were beneficial for neurological function, while sharp increases in NO metabolites from days 2 to 7 were associated with a doubling of infarct volume [40]. NO displays cytotoxicity by destroying cellular DNA, blocking mitochondrial activity, and enhancing nitrifying damage by forming peroxynitrite ($ONOO^-$) [41, 42]. NO is usually produced by endothelial nitric oxide synthase (eNOS). However, under inflammatory conditions, smooth muscle cells and macrophages overexpress inducible nitric oxide synthase (iNOS), thus producing large amounts of NO [43]. Moreover, NO is also produced by neuronal nitric oxide synthase (nNOS) [32, 40]. When it collides with NO, both molecules react quickly to form highly reactive $ONOO^-$[44]. Superoxide anions can also be dismutated into the more stable $H_2O_2$ through a reaction catalyzed by superoxide dismutase (SOD). In the central nervous system, $O_2^-$ is one of the most important reactive oxygen species as it damages ROS-producing cells and neighboring cells [43, 45]. Superoxide,

a byproduct of mitochondrial respiratory chain reactions, is the product of xanthine oxidase (XO) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activities [43, 46–48]. Interestingly, as the levels of superoxide increase, the NO radical has a dual effect. To be specific, NO interferes with SOD by reducing the antioxidant effect of SOD [43].

*2.2. Oxidative Stress in the Phases of Reperfusion.* The reperfusion of ischemic tissue has long been thought to be beneficial for tissue injury recovery. However, in the 1970s, reports of paradoxical enhancement of the injury response after ischemic (or hypoxic) tissue reperfusion (or reoxygenation) appeared, and the assumed beneficial effects of early reperfusion on tissue recovery after ischemia were questioned [49]. The question was solved when it was first found that the sudden resupply of molecular oxygen to energy-(and oxygen-) deficient tissues resulted in a special injury response not seen in hypoxic stress [50]. The discovery of this reoxygenation-dependent injury response, now known as "reperfusion injury," established a new field of scientific research that has since grown rapidly and continuously.

During reperfusion, the overproduction of ROS originates from four pathways: mitochondrial respiratory chain, cyclooxygenase-2-catalyzed arachidonic acid reaction, NADPH oxidase, and xanthine and hypoxanthine via xanthine oxidase (Figure 1). In the stage of early reperfusion, when microglia and other peripheral immune cells infiltrate, activation of NADPH oxidase in these immune cells contributes to the production of ROS, a phenomenon known as the "oxygen burst." NADPH oxidase also produces ROS in other cells, such as vascular endothelial cells [51]. When the blood flow is reinstated, a large amount of oxygen arrives and accelerates oxidative damage. Furthermore, oxidative stress during ischemia and reperfusion is known to activate proapoptotic signaling pathways such as cytochrome c signaling, induce DNA damage, alter protein structure and function, and induce lipid peroxidation [52–54]. In addition, oxidative stress can directly regulate important molecules in cellular signaling circuits, such as ion channels and protein kinases [55]. Over the past 25 years, researchers have found that hydrogen peroxide and possibly superoxide play a physiological role in cell signaling and transcriptional regulation [56]. Later research revealed that hydrogen peroxide is also produced under physiological conditions, e.g., in response to growth signals, and it can be overproduced in transformed cells expressing oncogenic mutant Ras [57]. ROS is produced in response to various ligands, including growth factors, cytokines, and G protein-coupled receptors [58, 59]. Therefore, during the recovery phase of reperfusion, low ROS concentrations play a key role in biotransduction signaling, which may be an important reason for promoting recovery from brain tissue damage during the recovery phase.

As displayed in Figure 1, NO and $ONOO^-$ are two common types of RNS frequently reported in cerebral ischemia-reperfusion injury. Low levels of NO, produced by endothelial nitric oxide synthase, have physiological functions; conversely, high levels of NO, produced by inducible nitric oxide synthase (NOS) and neuronal nitric oxide synthase (nNOS), have effects on ischemic brain tissue. iNOS and nNOS are known to lead to inflammation, cell death, increased blood-brain barrier permeability, and increased infarct size. During cerebral ischemia or cerebral ischemia-reperfusion injury, NO is produced simultaneously with superoxide anion ($O^{2-}$) and rapidly reacts with $O^{2-}$ at a diffusion-limited rate to generate $ONOO^-$. Peroxynitrite readily penetrates the lipid bilayer. It then impairs cell signaling by causing lipid peroxidation of the membrane, mediates nitration of tyrosine residues, and inhibits tyrosine phosphorylation. Peroxynitrite inactivates aconitase and superoxide dismutase, mediates NO-induced BBB damage, and triggers apoptotic cell death (Figure 1).

## 3. Roles of ncRNAs in Ischemia Stroke-Induced Oxidative Stress

*3.1. miRNA Involved in Oxidative Stress following Ischemia Stroke.* miRNAs, small noncoding RNA superfamily members, are endogenous single-stranded RNA molecules of about 18–25 nucleotides [60]. They act as negative regulators for more than 60% of protein-coding gene expressions by degrading or translationally inhibiting target mRNAs [61–63]. miRNAs can simultaneously modulate targets involved in the pathophysiological process of cerebral ischemia. Therefore, they are considered to have potential as diagnostic and prognostic biomarkers and promising therapeutics in treating ischemic stroke [64, 65]. miRNAs are produced as long primary transcripts (prior-miRNAs) and cleaved by Drosha RNase III endonuclease to result in dry ring intermediates (pre-miRNAs) of approximately 60 to 70 nucleotides [66]. The pre-miRNAs are then exported from the nucleus to the cytoplasm, where they are treated by Dicer RNase II endonucleases to form mature miRNAs of approximately 22–25 nucleotides [67]. Next, the mature miRNAs bind to multiprotein complexes called RNA-induced silencing complexes (RISC), which then bind to the $3'$-untranslated region (UTR) of their respective target mRNAs to inhibit translation [68]. Previous studies have found that miRNAs can be potential targets and modulators of oxidative stress-related pathways [69]. miRNAs associated with oxidative stress-related pathways are known as oxidative stress-responsive miRNAs [70]. Intracellular ROS can inhibit or promote miRNA expression and thus produce subsequent biological effects by regulating their direct target genes [71] (Figure 2).

The transient expression of miRNA was observed in blood and brain samples in the MCAO model after reperfusion. Additionally, miR-124a and -290 were upregulated after IR, targeted VSNL1 [72], encoded neuronal calcium sensor proteins in cerebellar granulosa cells, and regulated intracellular signaling pathways directly or indirectly by regulating cyclic nucleotide and MAPK pathways [73], therefore playing an active role in cell death, migration, and neuronal plasticity under pathological conditions such as stroke [74, 75]. Furthermore, miR30a-3p, -99a, -99b, -100, -223, and -383 were upregulated after IR and targeted

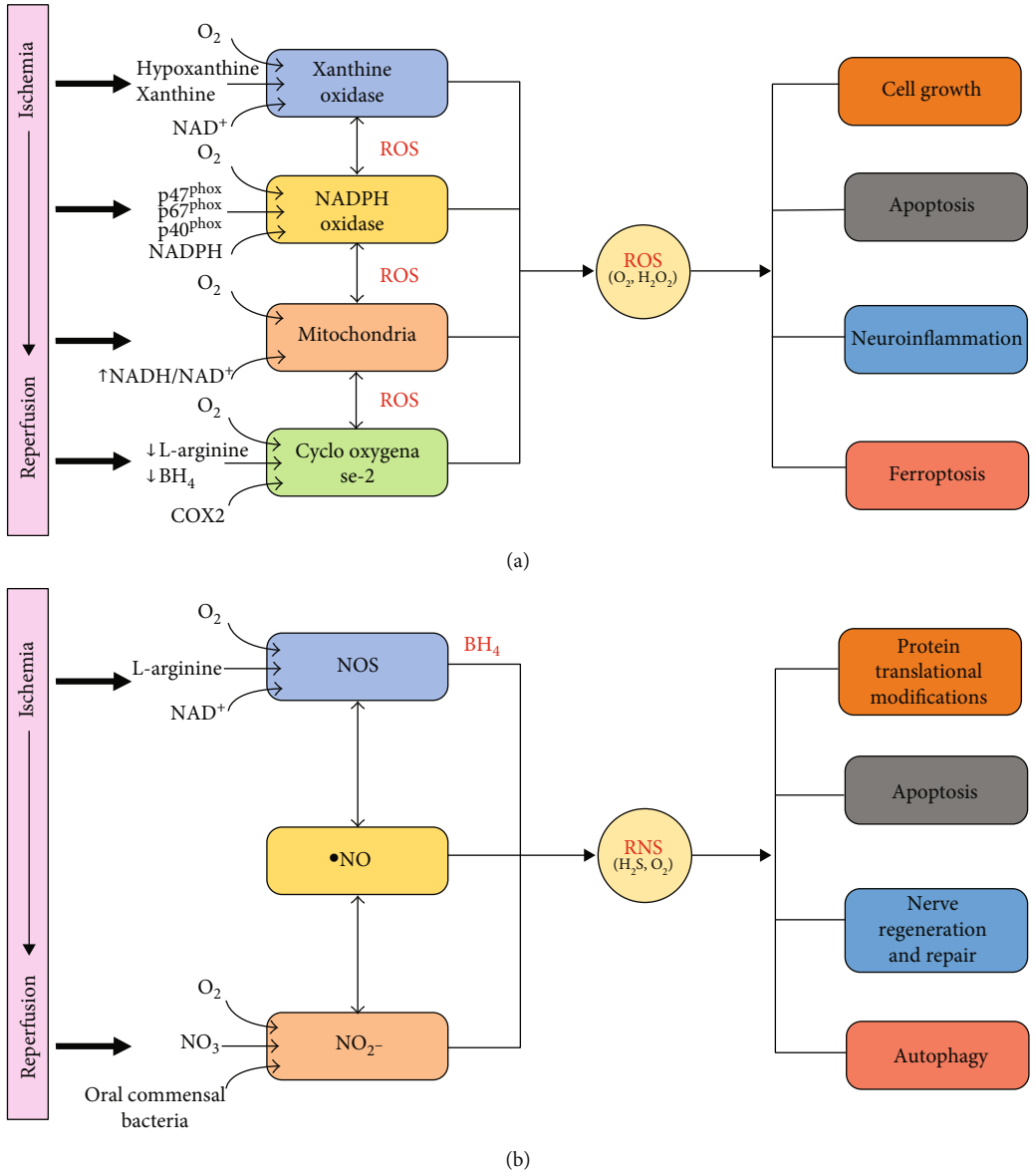


Figure 1: The sources of ROS and RNS during cerebral ischemia-reperfusion injury. During reperfusion, the overproduction of ROS originates from four pathways: mitochondrial respiratory chain, cyclooxygenase-2-catalyzed arachidonic acid reaction, NADPH oxidase, and xanthine and hypoxanthine via xanthine oxidase. In addition, NO and $ONOO^-$ are two common types of RNS that have been frequently reported in cerebral ischemia-reperfusion injury.

AQP4 [72], which was speculated to reduce cerebral edema due to its action as a water-selective channel in the plasma membrane of many cells and maintains cerebral hydrohomeostasis [76, 77]. miR-132 and -664 were downregulated after IR and targeted MMP9 [72], which disrupted the blood-brain barrier and caused cerebral edema. In addition, serum MMP-9 level was noted to be correlated with the severity of clinical stroke [78–80].

Based on transcriptome analysis, mitochondrial dysfunction and increased oxidative stress were the molecular mechanisms of miR-210 blockade, leading to increased tissue damage. While miR-210 can alleviate the decreased oxidative metabolism caused by tissue hypoxia, miR-210 also increases the accumulation of ROS, causing cell death and tissue damage [81–83]. However, in ischemic rats, the neuroprotective effects of decreased apoptosis and antioxidant stress response to vagus stimulation were associated with increased miR-210 expression. Protection decreased when miR-210 was blocked, thus suggesting that miR-210 is a neuroprotective factor against ischemia/reperfusion injury [84].

miR-124 is preferentially expressed in the cerebral cortex and cerebellum, initially at low levels in neural progenitors and subsequently at high levels in differentiated and mature neurons [85, 86]. In addition, miR-124 has been reported to protect PC12 cells from OGD/R-induced apoptosis by reducing oxidative stress via the PI3K/AKT/Nrf2 pathway [87]. Moreover, miR-124 enhances neurological recovery in various neurological illnesses by reducing oxidative stress after spinal cord damage via Bax [88, 89]. miR-124 inhibits inflammatory activation under oxidative stress and thereby

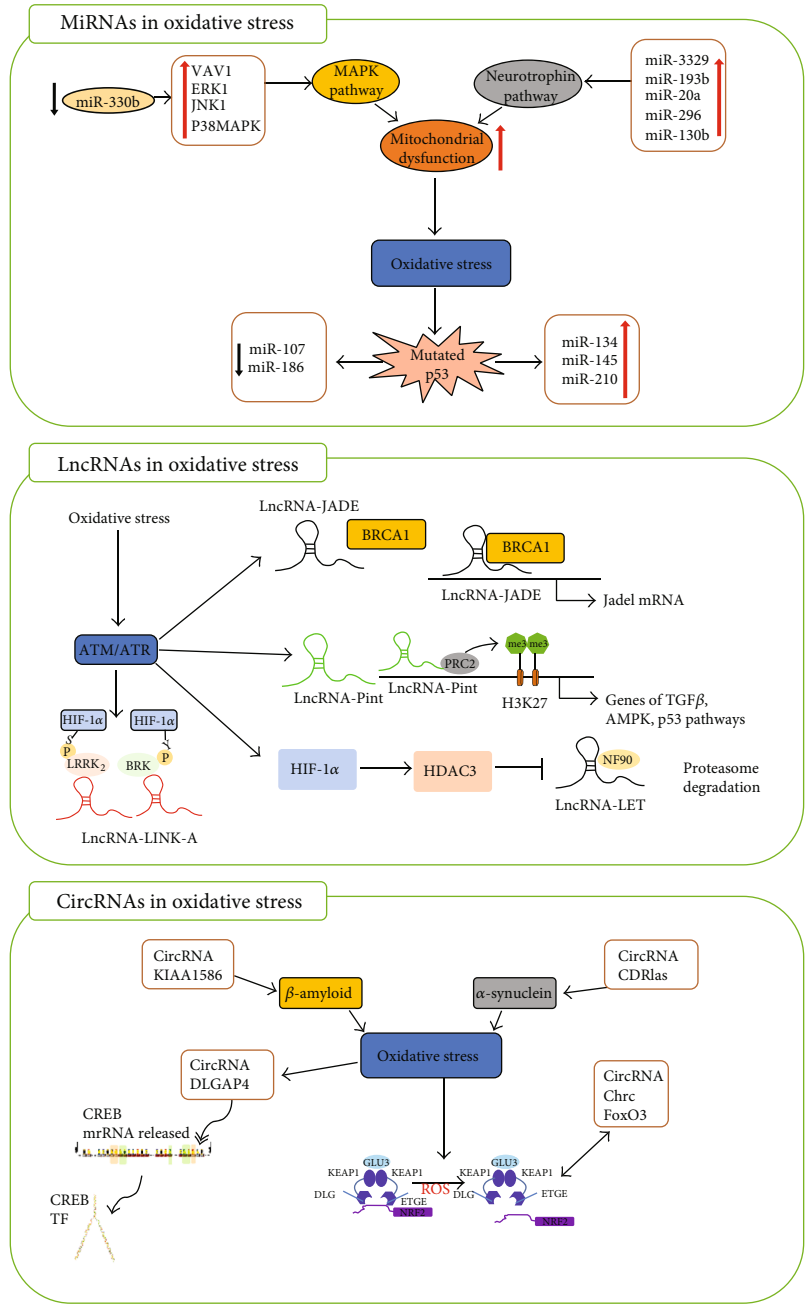


FIGURE 2: A mechanistic diagram of representative ncRNAs involved in oxidative stress under cerebral ischemia-reperfusion injury. Three different types of ncRNAs are involved in the mechanism of oxidative stress regulation in ischemic stroke, including oxidative stress induction, regulation, and effect. The ncRNAs in figure are taken as examples.

delays the progression of Alzheimer's disease (AD) [90]. These findings suggest that miR-124 is an important therapeutic target for inhibiting oxidative stress in ischemic stroke.

miR-217 is highly expressed in MCAO rats and the OGD cell model, and its expression level positively correlates with cognitive impairment in MCAO rats. miR-217 also deregulates MEF2D, regulates HDAC5 and ND6 expression, and promotes mitochondrial ROS production, thus leading to enhanced neuronal damage in ischemic stroke and IR [91].

*3.2. lncRNAs Involved in Oxidative Stress following Ischemia Stroke.* lncRNAs of more than 200 nucleotides are cell- and tissue-specific. These may be classified based on the genomic placement between the coding areas of their functional genes (long intergenic ncRNAs) or by coding gene overlap in either the consensus or antisense direction [92, 93]. As guides for chromatin modification complexes or transcription factors in the nucleus, cytoplasmic lncRNAs typically regulate mRNA translation by acting as competing endogenous RNA (ceRNA) or controlling mRNA stability [94]. Also, the lncRNA expression profile in the ischemic

penumbra was significantly altered after 1 h reperfusion in MCAO rats [95] (Figure 2).

In patients with ischemic stroke, lncRNA ZFAS1 is significantly downregulated [96, 97]. However, upregulated lncRNA-ZFAS1 can ameliorate brain injury in MCAO rats. It directly sponges miR-582 by promoting NOS3 expression and attenuating I/R-induced inflammation and cell apoptosis via oxidative stress. Studies have also mentioned that lncRNA-ZFAS1 can scavenge miR-186-5p by increasing the expression of the apoptosis regulator MCL1 and rescuing OGD-induced apoptosis of N2a cells [98].

lncRNA-H19 is a maternally derived gene on human chromosome 11. It is associated with stroke susceptibility in the Chinese population [99]. A previous study found that lncRNA-H19 was upregulated within 3 h after stroke, whereas levels of lncRNA-H19 were positively correlated with NIHSS scores of stroke patients within 3 h after stroke onset [100]. It demonstrated antioxidant capacity in metformin-mediated neuronal protection in ischemic stroke [101]. In the OGD/R model, inhibited lncRNA-H19 could reverse metformin-mediated SOD accumulation and MDA elimination [101]. This function was enabled by direct targeting of miR-148a-3p to regulate Rock2/HO-1/Nrf2 [101]. lncRNA-H19 also inhibited miR-19a and upregulated the inhibitor of DNA binding/differentiation 2 (Id2) that led to neuronal apoptosis induced by hypoxia [100].

lncRNA-SNHG14, also known as UBE3A-ATS, is an inhibitor of UBE3A, a brain-specific gene associated with neuronal development. It is involved in neuroinflammation after stroke [102]. lncRNA-SNHG14 promotes the accumulation of NO in microglia, leading to continuous activation of microglia, which causes apoptosis of neurons via the miR-145-5p/PLA2G4A axis [102]. Moreover, inhibition of lncRNA-SNHG14 SOD inhibits MDA accumulation and degradation in the BV-2 OGD model by regulating the miR-199b/AQP4 axis [103].

In lncRNA PVT1-inhibited MCAO rats, oxidative stress and neuron apoptosis were limited, and neurological impairments improved. In MCAO rats, the lncRNA PVT1 was activated by the sex-determining region Y-box 2 (SOX), sponged miR-24-3p, and regulated STAT3 expression [104].

In the SH-SY5Y OGD/R model, lncRNA SNHG15 was highly expressed and promoted the activation of oxidative stress signaling pathways by directly targeting miR-141/SIRT1 [105]. Moreover, miR-183-5p reversed lncRNA SNHG15-induced ROS accumulation in OGD/R-treated SH-SY5Y by directly targeting FOXO1 [106]. Furthermore, lncRNA SNHG15 retention reduced ROS accumulation in PC12 cells treated with OGD/R via the miR-455-3p/TP53INP1 axis [107].

Next, lncRNA OIP5-AS1 was downregulated in ischemic stroke patients, MCAO/R rats, and OGD/R-treated BV2 cells. Overexpression of OIP5-AS1 significantly decreased MDA accumulation, GSH, and overconsumption of SOD, thus counteracting neuroinflammation and oxidative stress and protecting neuronal injury by activating CTRP3 via sponging of miR-186-5p [108].

*3.3. circRNA Involves in Oxidative Stress after Ischemia Stroke.* circRNAs (single-stranded and conserved RNA molecules) are formed by the cleavage of many primary RNA transcripts that synthesize mRNA [109]. As they lack a well-defined 50- and 30-terminus [110], circRNAs can remain stable under the stress of RNase. circRNA regulates gene expression by various mechanisms, including functioning as a cornea through spongy miRNAs, forming ternary complexes with proteins, and encoding proteins [111–113]. circRNAs are abundant in brain tissue and involved in the development of vascular disease. Accordingly, they have been associated with neurological function [114] and acute ischemic stroke [115] (Figure 2).

Based on gene sequencing and KEGG analysis, circRyr2_23, circGucy1a2_7, circCamta1_9, circSmad4_4, and circDlgap3_1 play important roles in regulating oxidative stress by accessing Hif-1, Nrf, and VEGF signaling pathways [116]. The downregulation of circGucy1a2_7 and circRyr2_36 that occurs after stroke should spontaneously resist oxidative stress by adsorbing miR-7a5p to regulate Keap1/NRF-2 signaling [116–118].

circCCDC9 was downregulated in MCAO mice and remained at a low level for 72 h [119]. The upregulated circCCDC9 could restore eNOS expression, reduce oxidative stress, and protect the blood-brain barrier [119–121].

In patients with acute cerebral ischemic stroke, blood levels of circPHKA2 were downregulated. The same results were noted in human brain microvascular endothelial cells (HBMECs) treated with OGD [122]. Further studies confirmed that the upregulation of circPHKA2 decreased the accumulation of ROS and MDA, as well as increased SOD and GSH in OGD-HBMECs, which was due to the competitive binding of miR-574-5p to modulate SOD2 [122].

Various studies on microarrays and sequencing analyses have reported abnormal circRNA expression in ischemic stroke. Furthermore, analyses of Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) recalled these circRNAs to be prominent in neuroinflammation, apoptosis, and oxidative stress [123]. However, a few studies have explained the mechanism of circRNA involvement in oxidative stress after ischemic stroke, which has also been explored in other diseases [124] (Table 1).

## 4. Noncoding RNA Therapy for Ischemic Stroke

It is extremely important to find objective and effective biomarkers for stroke, because these indicators can not only help the early diagnosis and prognosis assessment of stroke but also serve as therapeutic targets to assist the development of new drugs. Universality, stroke can cause cascade changes of chemicals and transcripts in brain tissue, while conserved expression, defined specificity, high stability, and abundance are the main characteristics of ncRNAs that render them very attractive diagnostic tools for assessing diseases. Thus far, studies have demonstrated the potential of ncRNAs as a cancer diagnostic marker, and recently, studies have shown that ncRNA is also a potential diagnostic marker for neurodegenerative diseases [92, 125, 126].

Table 1: A list of ncRNAs involved in oxidative stress under cerebral ischemia-reperfusion injury.

| ncRNAs | Functions | References |
|---|---|---|
| miRNA | | |
| miR-124a | Encoding neuronal calcium sensor proteins in cerebellar granulosa cells | [68, 70] |
| miR-290 | Regulating cyclic nucleotide and MAPK pathways | [69, 71] |
| miR30a-3p | Migration and neuronal plasticity | [72] |
| miR-99 | Regulates AQP4 | [73] |
| miR-100 | Connects the DNA damage response to histone H4 acetylation | [74] |
| miR-223 | Regulates serum MMP-9 level | [75] |
| miR-383 | Regulates AQP4 and causes cerebral edema | [76] |
| FmiR-132 | Involves the blood-brain barrier disruption | [70] |
| miR-210 | Alleviates the decreased oxidative metabolism caused by tissue hypoxia | [79–81] |
| miR-124 | Protects PC12 cells from OGD/R-induced apoptosis by reducing oxidative stress via the PI3K/AKT/Nrf2 pathway | [83–85] |
| miR-217 | Deregulates MEF2D, regulates the expression of HDAC5 and ND6, and promotes mitochondrial ROS production | [89] |
| lncRNAs | | |
| lncRNA ZFAS1 | Downregulated by oxidative stress | [93, 94] |
| ANRIL | Represses the expression of INK4A-ARF-INK4B | [96] |
| lncRNA-H19 | Reverses metformin-mediated SOD accumulation and MDA elimination | [98, 99] |
| lncRNA-SNHG14 | Promotes accumulation of NO in microglia, leading to continuous activation of microglia | [99, 100] |
| lncRNA PVT1 | Regulated STAT3 expression and activated by the sex-determining region Y-box 2 (SOX) | [101] |
| lncRNA SNHG15 | Reduces ROS accumulation of PC12 cells treated with OGD/R via the miR-455-3p/TP53INP1 axis | [102–104] |
| lncRNA OIP5-AS1 | Protecting neuronal injury by activating CTRP3 via sponging miR-186-5p | [105] |
| circRNAs | | |
| circCCDC9 | Restores eNOS expression, reduces oxidative stress, and protects the blood-brain barrier | [106–108] |
| circPHKA2 | Decreases the accumulation of ROS and MDA and increases SOD by competitive binding miR-574-5p | [109] |

In the past few years, several in vivo and in vitro studies have demonstrated that certain ncRNAs change over time after ischemic stroke, and they are expected to be widely used as biomarkers in clinical practice. The observed variations in ncRNA amounts in blood samples could be helpful biomarkers that reflect the pathophysiological state of the brain, thus implying that circulating ncRNAs have potential prospects. In addition, Dykstra-Aiello et al. [127] discovered aberrant ncRNA expression in peripheral blood of stroke patients with sex differences, suggesting that certain ncRNAs may be useful biomarkers for stroke development. Wang et al. [128] investigated patients with ischemic stroke and reported that mutations in the H19 gene increased the risk of ischemic stroke. Another independent study revealed that lncRNA H19 levels were significantly increased in the blood and cytoplasm of stroke patients, with high diagnostic sensitivity and specificity levels. This indicates that lncRNA H19 may be a novel diagnostic and therapeutic target for ischemic stroke. Moreover, Mehta et al. [129] suggested that lncRNA FosDT could reduce the loss of motor function after cerebral infarction and stroke via the regulation of REST downstream genes.

In clinical practice, noncoding RNAs are abnormally expressed in the blood of ischemic stroke patients and are closely related to patient prognosis. In whole blood, studies have found that miR-122, miR-148a, let-7i, miR-19a, miR-320d, and miR-4429 are downregulated, while miR-363 and miR-487b are upregulated [130]. Moreover, Lu et al. [131] put forward the idea of noncoding RNAs as potential clinical biomarkers for disorders in the CNS. They suggest that noncoding RNAs can regulate CNS function and many diseases and can be used as a potential biomarker for the diagnosis and prognosis of CNS diseases, as well as combined with other biomarkers and imaging tools to improve the diagnostic power. Subsequently, Mehta et al. [16] conducted a comprehensive circRNA expression profile analysis on male tMCAO mice. microRNA-binding sites, transcription factor binding and gene ontology of circRNAs altered after ischemia were determined under cerebral ischemia. In their study, a total of 1322 detectable circRNAs were comprehensively analysed, of which 283 had significant changes. Their research shows that these noncoding RNAs altered after stroke may be controlled by a set of transcription factors. These noncoding RNAs are involved in many processes and functions such as biological regulation, metabolism, cell communication, and binding with proteins, ions, and nucleic acids. Liu et al. [132] also studied the expression profile of ncRNAs in ischemic stroke and confirmed that noncoding RNA is a potential target for diagnosis and treatment of stroke.

Current research has discovered the role of certain functional ncRNAs such as lncRNA H19 and MALAT1 in ischemic stroke. However, research on ncRNAs still faces many challenges. For example, it is difficult to study their molecular mechanisms due to the complexity of the various functions of ncRNAs. Furthermore, many ncRNAs are expressed only in primates. Even though a significant part of the molecular mechanism has been identified, there is still a long way to go before it can be implemented in clinical use.

## 5. Conclusion

In this review, the mechanisms of oxidative stress in ischemic stroke and reperfusion injury were discussed, alongside the involvement of ncRNAs in the pathological process. Additionally, the potential of three types of ncRNAs for treating stroke was explored. With advances in clinical and experimental techniques, continued research into ncRNAs and their pathways could likely lead to developing a new treatment for ischemic stroke.

## Conflicts of Interest

The authors declare that they have no competing interests.

## Authors' Contributions

Zhongzhou Su and Yingze Ye contributed equally to this work.

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