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Hypoxia related long non-coding RNAs in ischemic stroke

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ABSTRACT

With high rates of mortality and disability, stroke has caused huge social burden, and 85% of which is ischemic stroke. In recent years, it is a progressive discovery of long non-coding RNA (lncRNA) playing an important regulatory role throughout ischemic stroke. Hypoxia, generated from reduction or interruption of cerebral blood flow, leads to changes in lncRNA expression, which then influence disease progression. Therefore, we reviewed studies on expression of hypoxia-related lncRNAs and relevant molecular mechanism in ischemic stroke. Considering that hypoxia-inducible factor (HIF) is a crucial regulator in hypoxic progress, we mainly focus on the HIF-related lncRNA which regulates the expression of HIF or is regulated by HIF, further reveal their pathogenesis and adaption after brain ischemia and hypoxia, so as to find effective biomarker and therapeutic targets.

1. Introduction

Stroke with high disability rate is one of the leading causes of death in the world. It resulted in significant loss of health and economy [1]. Ischemic stroke (IS) accounts for about 85% of all kinds of stroke [2]. As results of various intracranial artery system obstruction, reduction of cerebral blood flow and tissue hypoxia lead to dysfunction of ion channels. The consequent excitotoxicity, oxidative stress and inflammation eventually result in dysfunction of brain tissue [3]. So far, although the treatment of IS is constantly improved, the incomplete understanding of molecular regulatory in the occurrence and development of IS still limit the studies of relevant therapy. In recent years, high-throughput sequencing has facilitated the research of non-coding RNAs (ncRNAs) [4]. NcRNAs are found to be typically involved in the molecular regulation of occurrence and development of IS.

Long noncoding RNA (lncRNAs) are comprised of diverse noncoding RNAs that are longer than 200 nucleotides, which are widely involved in the regulation of gene expression [5]. On the one hand, lncRNAs can conduct direct regulation on epigenetic, transcriptional, post-transcriptional, and chromatin remodeling level through RNA splicing and other processes [6]. On the other hand, acting as competing endogenous RNAs (ceRNAs), lncRNAs can also interact with microRNA (miRNAs) in order to regulate the target protein [7]. Except for the function of multi-level regulation, lncRNAs are widely involved in biological processes such as cell proliferation, differentiation, apoptosis, autophagy, immune response and angiogenesis [8]. Therefore, lncRNAs play a crucial role in the molecular regulatory network. According to the previous studies on IS, lncRNAs level in neural tissue significantly changed after ischemia and hypoxia [9]. In fact, similar changes have already appeared in the early stages [10]. Studies revealed that hypoxia-related lncRNAs were closely related to the regulation of injury patterns such as inflammation and oxidative stress, suggesting hypoxia-related lncRNAs to be an important role in the occurrence and development of IS [8]. Therefore, the exploration of hypoxia-related lncRNAs may be conductive to searching for biomarkers related to diagnosis and prognosis, and contribute to the targeted and individualized treatment of IS.

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1.1. The classification of lncRNA

The lncRNA is transcribed from the sequence of the non-coding region of DNA [11]. According to different positional relationships on the genome, lncRNA can be roughly divided into five categories, intron, intergenic, bidirectional, sense and antisense lncRNA [12]. Intron lncRNA is transcribed from DNA sequences that intercept gene sequences. From a mechanism point of view, most intronic lncRNAs have the same tissue expression pattern, which can induce and regulate the transcription and splicing of coding genes [13,14]. Intergenic lncRNA is transcribed from DNA fragments located between genes, and affects the expression of closely related genes by controlling the promoter and enhancer of the gene [15]. Bidirectional lncRNA is a lncRNA whose two ends are transcribed in opposite directions and mainly participates in the transcription process of DNA through functions similar to protein coding substances [16]. Sense lncRNA is transcribed from the DNA strand s which encode the exon, while antisense lncRNA is transcribed from the antisense protein encoding gene. These lncRNAs act as regulators in the process of gene expression through overlapping and covering protein-coding genes, and play important roles during physiological and pathological course [17,18].

1.2. The mechanism by which lncRNA works

In order to realize how lncRNAs work, we make a brief summarize in Fig. 1. As is shown, lncRNAs can manipulate gene expression at the transcription and post-transcription level. At the transcriptional level, lncRNAs adjust gene expression through regulation and modification of relative chromosomes. At the post-transcriptional level, in addition to producing miRNA and degrading mRNA, some lncRNAs work as ceRNAs to influence gene expression [19], Here shows the major mechanisms lncRNA works:

1) First, at the transcription level, lncRNA supports and recruits different kinds of chromatin regulatory proteins, meanwhile, they recognize and interact with chromatin at specific sites through three-dimensional (3D) proximity or affinity methods. With integration and arrangement of shapes of chromosome, lncRNAs could inhibit or promote acetylation or methylation, and consequently activate chromosomal alteration and gene expression [20].
2) At the post-transcriptional level, lncRNA can directly regulate gene expression by controlling RNA splicing, the step of transcription from precursor mRNA into mRNA. lncRNA binds to the precursor mRNA and blocks the binding of the spliceosome to the target sequence, resulting in the formation of splice variants.
3) lncRNA is also part of the sources of miRNA. The evidence is that there are embedded miRNA sequences in the introns and exons of many lncRNA genes.
4) Some lncRNAs act as miRNA sponge on account of their complementary binding sites with certain miRNAs. They serve as ceRNAs to reduce the concentration of target miRNAs, which finally inhibit the function of miRNAs in cells [21,22].
5) LncRNA can also directly bind to mRNA and regulate mRNA degradation [23].

1.3. The significance on the research of lncRNA

With the increasing maturity of high-throughput methods, the functions of lncRNA in various diseases have been gradually revealed. In IS, the expression of a variety of lncRNA changes, and these changed LncRNAs have been reported to play an important role [19,24]. Guo et al. detected 560 up-regulated and 690 down-regulated lncRNAs in the peripheral blood of patients with IS through the chip and constructed their regulatory network. Their target genes were significantly enriched in signaling pathways such as PI3K Akt signaling pathway, Wnt signaling pathway, and MAPK signaling pathway [25]. Previous studies have shown that these signaling pathways are involved in the pathological process of IS [26–28]. Yang et al. compared the expression of lncRNA between 550 patients with IS and the same amount of healthy people and found that the overexpression of lncRNA ANRIL and the

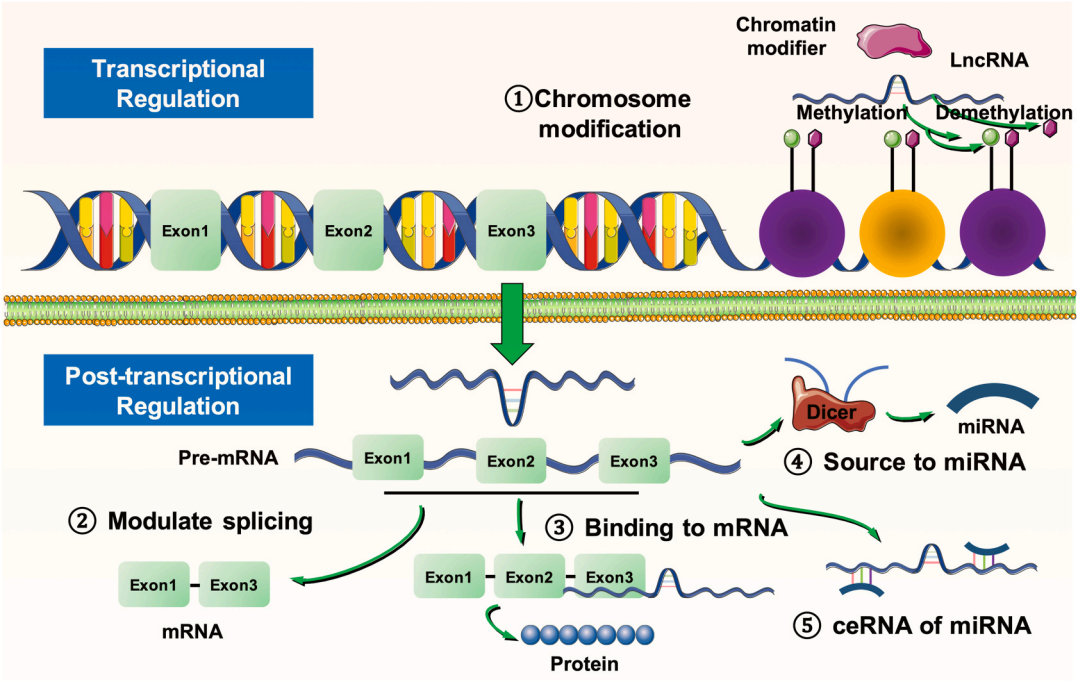

Fig. 1. The mechanism of lncRNA function. 1, Chromatin modification. 2, Shearing of pre-mRNA. lncRNA binds to pre-mRNA and blocks the binding of the spliceosome to the target sequence, resulting in the formation of splice variants. 3, Binding to mRNA and affect its stability or translation. 4, Serve as one of the sources of miRNA. Many lncRNA genes contain embedded miRNA sequences in their introns or exons. 5, CeRNA of miRNA. Some lncRNAs contain complementary binding sites with certain miRNAs, thereby absorbing target miRNAs and leading to reduced miRNA functions in cells.

decrease of lncRNA CDKN2A expression may promote the pathological process of IS [29]. By comparing the expression of lncRNA in peripheral blood between 189 patients with IS and a matched control group, Zhu et al. found that the expression of lncRNA MIATDE in peripheral blood leukocytes was significantly higher and resulted in a larger infarct area and a worse prognosis [30]. In addition to changes in the expression of lncRNA, the genetic polymorphism of lncRNA is also closely related to the poor prognosis of IS. For example, the genetic polymorphism rs1194338 of LncRNA MALAT1 leads to a lower risk of in IS patients [24]. The rs224 0183 CT/CC genotype of the lncRNA TUG1 promoter is associated with a high risk of IS [31]. These findings mark that we have discovered a large number of ischemia-responsive lncRNAs.

Meanwhile, at the animal level, some researchers have reported the evaluation of lncRNA expression in the cortex of mice after IS under deep sequencing. In a rat model of spontaneous hypertension with transient focal ischemia, the researchers assessed the expression levels of a total of 8314 lncRNAs using microarrays, and found that 443 lncRNAs differed between the experimental group and the control group at 3–12h of reperfusion [32]. Moreover , researchers found the expression of lncRNA also changed in the study of cerebral blood vessels and blood circulation after stroke, Someone used RNA-seq to evaluate the gene expression of mouse primary brain microvascular endothelial cells (BMEC) after glucose-oxygen deprivation (OGD). It was found that compared with the normal oxygen control group, there were 362 lncRNAs with different changes. After performing real-time PCR on the lncRNAs isolated from microvessels of the mouse cerebral cortex after the middle cerebral artery occlusion, some of the findings have been basically verified [33]. Later studies on endothelial cells in vitro and in vivo showed that several lncRNAs that change after ischemia are involved in important post-stroke pathological processes, such as inflammation, cell survival and angiogenesis [34–36].

These studies have shown that IS induces extensive changes in the expression of lncRNAs in the brain and blood, especially in the pathological model of glucose and oxygen deprivation. The changed lncRNA has obvious expression characteristics. This phenomenon led us to focus on lncRNAs associated with reduced oxygen supply to the brain.

1.4. Hypoxia related lncRNAs involved in ischemic stroke

Due to insufficiency of regional transient or permanent blood supply, local brain tissue has insufficient oxygen supply [37]. Thus, a series of pathophysiological changes appear after hypoxia, such as oxidative stress, inflammation, necrosis and apoptosis of cells, etc [38]. The most central role involved in the regulation of hypoxia is the hypoxia-inducible factor (HIF). HIF is a gene that changes its expression and functional state according to the microenvironment with different oxygen levels in the cell, thereby regulating the cell's oxygen homeostasis and metabolism [39]. HIF is a heterodimer composed of an α subunit and a β subunit. The β subunit is stably expressed in the nucleus, and the α subunit is expressed in the cytoplasm and is regulated by oxygen content [40]. The difference in α subunits can constitute three different transcripts, HIF-1α, HIF-2α, and HIF-3α, between which HIF-1α and HIF-2α have 48% sequence homology. However, they play a role in different situations. HIF-1α mainly plays a role in acute hypoxia, and HIF-2α mainly plays a role in chronic hypoxia. The role of HIF-3α is not yet clear [41]. HIF can achieve its regulatory functions by regulating various pathophysiological processes, such as oxygen consumption, angiogenesis, inflammation and so on [42]. These pathological processes all play an important role in IS. Moreover, studies have shown that there are a variety of lncRNAs that can regulate the process of hypoxia by interacting with HIF. In this review, we divide the function of lncRNAs related to HIF in hypoxia in IS into two parts to explain, one is the lncRNAs that regulate the expression of HIF, and the other part of it is the lncRNAs regulated by HIF.

1.5. H19

H19 gene can be transcribed to produce a 2.3 kb non-coding RNA, which is an imprinting lncRNA [43]. It is expressed during embryonic development and down-regulated after birth. Under hypoxia, the expression of H19 can be induced again through the HIF1α signaling pathway [44]. Various studies have reported that lncRNA H9 plays an important role in a variety of inflammatory mechanisms. For example, NFκB, p38/MAPK/mTOR, toll-like receptor, and TNF-a [45]. At the same time, H19 also regulates neuronal apoptosis and oxidative stress [46]. In addition, H19 polymorphisms are also associated with a variety of IS and their underlying diseases. In the Chinese population, 701 patients with coronary heart disease and 873 control samples matching their characteristics were compared and analyzed. There is a link between sex and the risk of coronary heart disease [47]. Huang's research shows that H19 gene polymorphism is not related to the risk of IS but is closely related to blood pressure, coagulation function, and homocysteine metabolism, which are risk factors for IS [48]. However, Huang's study has reached a different conclusion. The polymorphism of H19 rs217727 leads to a higher risk of IS [49]. This may be because the subjects of the two studies are Chinese and Iranian. H19 seems not playing the same role in IS in different ethnic groups, but they both directly or indirectly cause IS and the patients' poor prognosis. Excluding the polymorphic IS of H19 plays an important role, the overexpression of H19 also plays a key regulatory role in IS. The overexpression of H19 can reduce the expression of its downstream target notch1 by inhibiting the activity of p53, which negatively affects nerve repair [50]. Inhibiting the overexpression of H19 in IS can activate the IGF1-mediated mTOR pathway through the overexpression of IGF1R, thereby promoting the sprouting of neuronal axons and the recovery of autonomous movement, and improving the prognosis of patients [51]. In addition, the inflammatory regulation effect of H19 in IS can be reflected in its regulation of TNF-α and other inflammatory factors, and injection of H19 siRNA into the lateral ventricle can reduce the scope of infarction and the degree of cerebral edema, possibly by regulating HDAC1 depending on the polarity of M1 microglia [52]. Aspirin is most commonly used for the treatment of IS. Its efficacy is not completely same in different patients due to the different expression levels of H19 in different patients. Higher levels of H19 induce aspirin resistance leading to worse treatment effect for patients [53]. In summary, the expression of H19 is regulated by HIF-1α, and H19 is associated with a variety of pathophysiological processes of IS, including inflammation, oxidative stress, and drug resistance. In addition, studies have also shown that H19 can adsorb miR-138 through the ceRNA mechanism to further regulate HIF-1α and ultimately promote angiogenesis [54]. However, this mutual regulation relationship between H19 and HIF needs further proof in IS.

1.6. MALAT1

lncRNA MALAT1 is transcribed by RNA polymerase II and is regulated by the environment at both the transcription level and the post-transcription level [55]. Under hypoxia, HIF can up-regulate the expression of MALAT1 by activating pre-bound promoter-paused RNA-pol2 [56]. The expression of MALAT1 in endothelial cells regulates a variety of pathophysiological processes related to cardiovascular and cerebrovascular diseases, such as oxidative stress, autophagy, and apoptosis [57,58]. This is closely related to the variable splicing, transcription or post-transcriptional level involved in the expression of multiple proteins [8,59]. In patients with IS, the MALAT1 low expression group and the higher expression group have a longer recurrence-free survival trend, and it regulates the expression of a variety of inflammatory factors, such as TNF-α, IL-6, IL -8, etc [60]. In IS, MALAT1 can regulate the expression of miR-205–3p through the ceRNA mechanism to further regulate the expression of downstream target gene PTEN, and ultimately affect cell apoptosis in IS [61]. In addition, the ceRNA mechanism also exists in the MALAT1-miR-30a-Beclin1 axis.

Knockdown of MALAT1 can reduce Beclin1-dependent cell apoptosis, thereby reducing cell death [62]. In order to better understand the expression of MALAT1 in IS tissues, we simulated the middle cerebral artery occlusion/reperfusion (MCAO/R) model of mice. The results showed that the expression of MALAT1 increased, and play a role through the regulation of the MDM2/p53 axis, while knocking down MALAT1 can increase cell proliferation and reduce the area of infarction [63]. Similar to the mechanism of action between H19 and HIF and the positive regulation of MALAT1 by HIF, MALAT1 can also activate the HIF-1α pathway [64]. Therefore, MALAT1 can be used as a potential clinical treatment target, but further research is still needed to clarify the mechanism of action between it and HIF.

1.7. UCA1

lncRNA UCA1 was initially being found in bladder cancer, and it is normally only expressed during embryonic development but almost not expressed in mature individuals [65]. Xue's research pointed out that HIF-1α can bind to hypoxia response elements (HREs) in the promoter region of lncRNA UCA1, thereby regulating the expression of lncRNA UCA1 under hypoxic conditions [66]. A number of studies have shown that lncRNA UCA1 plays an essential role in regulating the expression of various inflammatory factors and the pathophysiological process of various strokes. When the expression of lncRNA UCA1 is down-regulated, it plays a role in inhibiting inflammation and neuroprotection. On the contrary, the over-expression of lncRNA UCA1 mediates the damage to nerves. In lipopolysaccharide-induced sepsis, lncRNA UCA1 can regulate the inflammatory response by regulating many inflammatory-related factors, such as interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [67]. In Parkinson's disease patients, the expression level of lncRNA UCA1 decreases, which leads to the inhibition of neuroinflammation and oxidative stress mediated by the PI3K/Akt signaling pathway, thereby protecting neurons [68]. Similarly, Tian's research shows that in stroke, the up-regulation of lncRNA UCA1 expression mediates brain damage, which is achieved by inhibiting miR-18a, which leads to the increase of the expression level of its target gene SOX6 [69]. The latest research reports that the overexpression of lncRNA UCA1 predicts a worse prognosis in stroke patients [70]. This is consistent with previous research. Therefore, lncRNA UCA1, as a lncRNA regulated by HIF, plays a vital role in stroke.

1.8. SNHG1

lncRNA SNHG1 is a lncRNA that can regulate HIF expression under hypoxic conditions. SNHG1 is overexpressed under OGD conditions. Silencing SNHG1 will down-regulate Bcl-1, HIF-1α and VEGF-A, thereby aggravating hypoxia and cell apoptosis under conditions [71]. The protective effect of SNHG1 in IS has been confirmed in many studies. LV studies have shown that SNHG1 is highly expressed in IS and is combined with miR-376a through the ceRNA mechanism to improve the prognosis of IS patients [72]. Zhang's research shows that the overexpression of SNHG1 in IS inhibits the expression of miR-18a and further affects the expression level of HIF-1α, thereby achieving the protective effect of SNHG1 under hypoxic conditions [73]. Liang's research confirmed that SNHG1 can also be used for miR-140–3p through ceRNA mechanism, and HIF-1α is used as a target of miR-140–3p. Therefore, SNHG1 can finally achieve the regulation of HIF for IS and promote angiogenesis, cell proliferation, cell migration, etc [74].

1.10. MEG3

MEG3 is an imprinted gene. It transcribes lncRNA MEG3, which is missing in many tumors. Its re-expression can inhibit tumor cell proliferation and invasion [80]. It shows that it plays an essential role in the process of regulating cell proliferation. lncRNA MEG3 can also regulate HIF through variety of ways, thereby participating in the pathophysiological process of IS. Inhibition of MEG3 can reduce its binding to the transcription factor c-Jun. Furthermore, the expression of c-Jun transcription factor-dependent PHPP1 is reduced, which ultimately leads to the reduction of PHPP1-mediated HIF translation [81]. Under hypoxia, the effect of silencing MEG3 and HIF's competitive binding to microRNA-135a is weakened, thereby enhancing the inhibitory effect of microRNA-135a on HIF, reducing HIF expression, and ultimately promoting cell proliferation and inhibiting apoptosis [82]. The expression of MEG3 in IS is positively correlated with the infarct size of the patient, leading to a poor prognosis of the patient [83]. Its regulatory effect is closely related to its regulation of MiR-378/GRB2 axis, MAPK signaling pathway, and polymorphism of 181b rs322931 [84–86]. However, there is still a lack of direct evidence on whether HIF is involved in these processes.

1.9. NEAT1

lncRNA NEAT1 consists of two transcripts, NEAT1v1 (3.7 kb) and NEAT1v2 (23 kb), and plays a role in a variety of diseases, such as viral infections, tumors, Parkinson's disease, etc [75]. A number of studies have revealed the different regulatory effects between NEAT1 and HIF. Under hypoxic conditions, NEAT1 can regulate the expression of HIF-2α [76]. The expression of HIF-1α can also be regulated by miR-186–5p [77]. In addition, studies have also revealed that HIF-2α can also regulate the expression of NEAT1 [78]. Similarly, silencing HIF-1α can also down-regulate NEAT1 expression [79]. NEAT1 revolves around the regulation of HIF, making it play an important role in IS. In IS, the overexpression of NEAT1 leads to a higher level of the inflammatory response, including the increase of inflammatory factor c-reactive protein, IL-6, IL-8, etc., and the decrease of inflammation negative regulator IL-10. High levels of NEAT1 is associated with shorter recurrence-free survival (RFS).

2. Conclusion and future perspectives

LncRNAs play a key role in IS. They can regulate a variety of pathophysiological processes in IS. As the core regulatory factor of IS, HIF can regulate the expression of various lncRNAs, such as H19, MALAT1, UCA1, etc. At the same time, the expression of HIF is also regulated by various lncRNAs in IS, such as SNHG1, NEAT1, MEG3, etc. In addition, some lncRNAs can not only regulate the expression of HIF, but also change their own expression according to the state of HIF, such as H19, MALAT1, etc. Therefore, a regulatory network with HIF as the core is formed in IS, a further insight into this complex interplay will help reveal the hypoxia-related lncRNA in IS.

With the continuous research on hypoxia-related lncRNAs, a more comprehensive mechanism network which is conducive to the screening of efficient targets can be generated, and provide a better guidance for the clinical application transformation of hypoxia-related lncRNAs. Besides, the discovery of lncRNA-encoded short peptides also shed light on the study of hypoxia-related lncRNAs [87]. As the basic research on hypoxia-related lncRNA gradually shifting to clinical research in the future, it is worth looking forward to providing effective biomarkers and therapeutic targets for the diagnosis and treatment of IS.

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Declaration of competing interest

The authors declare no conflict of interest.

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