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REVIEW ARTICLE

Long non-coding RNAs and cell death following ischemic stroke

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Abstract

Stroke is a major cause of morbidity and mortality worldwide, and extensive efforts have focused on the improvement of therapeutic strategies to reduce cell death following ischemic stroke. Uncovering the cellular and molecular pathophysiological processes in ischemic stroke have been a top priority. Long noncoding RNAs (lncRNAs) are endogenous molecules that play key roles in the pathophysiology of cerebral ischemia, and involved in the neuronal cell death during ischemic stroke. In recent years, a bulk of aberrantly expressed lncRNAs have been screened out in ischemic stroke insulted animals. LncRNAs along with their targets could affect the genetic machinery at molecular levels, and exploring their functions and mechanisms may be a promising option for ischemic stroke treatment. In this review, we summarize the current knowledge for lncRNAs in ischemic stroke, focusing on the role of specific lncRNAs that may underlie cell death to find possible therapeutic targets.

Keywords Long non-coding RNA · Ischemic stroke · Cell death

Introduction

Stroke is a major health problem worldwide, and the second most common cause of death and the third leading cause of disability (Feigin et al. 2017). Stroke accounts for 5.5 million deaths annually, with 44 million disabilities worldwide (Huang et al. 2012). According to the current global burden of disease data on stroke, in 2013 there were almost 25.7 million stroke survivors, 6.5 million deaths, 113 million disability-adjusted life year (*DALY*) due to stroke, and 10.3 million new strokes (Donkor 2018; Moran et al. 2013). The burden of stroke seems to be shifting to the developing world where currently, there are 4.85 million stroke deaths and 91.4 million DALYs annually compared with 1.6 million deaths and 21.5 million DALYs in high-income countries (Donkor 2018; Moran et al. 2013).

Numerous efforts have been made to restore neurological function and reduce ischemia-induced neuronal injury, including inhibition of *N*-methyl-*D*-aspartate (NMDA) receptor (Yu et al. 2015), repression of neuroinflammation (Hawkins et al. 2017), opening of the K_{ATP} channel (Sun et al. 2015), suppression melastatin-like transient receptor potential cation channel, subfamily M, member 7 (TRPM7) channel (Sun et al. 2009), and inhibition of postsynaptic density-95 (Sun et al. 2008). Despite this, rtPA (a thrombolytic agent) is the only FDA-approved specific pharmacotherapy for the acute phase of ischemic stroke (Tan et al. 2014). Furthermore, it has been shown that intravenous thrombolysis could be an effective intervention to restore perfusion to cerebral tissue (Tekle et al. 2012). However, this form of intervention is limited due to a narrow therapeutic window (Group I-C 2012). The neuroprotective strategies after ischemic stroke could be so far additive to reperfusion-recanalization methods, but these

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neuroprotective agents failed in clinical trials due to deleterious side effects and/or low efficacy (Khoshnam et al. 2018a; Khoshnam et al. 2017a; Khoshnam et al. 2018b; Van der Worp et al. 2002). Therefore, there is an urgent need for novel and promising therapeutic targets. Undoubtedly, a better understanding of the pathological mechanisms will contribute to improve effective treatment for ischemic stroke.

Long non-coding RNAs (lncRNAs) are constitute a significant portion of the mammalian genome, and are widely involved in basic biological processes such as cell proliferation, differentiation, apoptosis, autophagy, immune responses, and angiogenesis. However, the functions and underlying mechanisms of lncRNAs during pathophysiological processes of ischemic stroke are not fully known (Carpenter et al. 2013; Mercer et al. 2009; Schaukowitch and Kim 2014; Yang et al. 2012). LncRNAs may act as competing endogenous RNAs (ceRNAs), namely, micro RNA (miRNA) sponges or antagomirs, which interact with miRNAs and regulate the expression of miRNA target protein (Han et al. 2015; Tang et al. 2015; Wang et al. 2016; Xiao et al. 2015). It has been reported that lncRNAs are involved in ischemic stroke and mediate ischemic neuronal death in stroke (Wu et al. 2017; Yan et al. 2016). Following cerebral ischemia, lncRNA transcriptomic profiles are altered in the brain microvascular endothelium (Zhang et al. 2016). Previously it was shown that lncRNAs play an important role in regulating the expression of proteins at multiple levels (Lorenzen et al. 2012). Numerous classes of molecules such as lncRNAs underlying pathological mechanisms after ischemic stroke, cannot be ignored. LncRNAs are estimated to become a new modality and target in regulation of ischemic stroke pathogenesis. This review focusses on the functions of specific lncRNAs underling neuronal apoptosis and cell death following ischemic stroke to reveal possible therapeutic targets.

Ischemic stroke

Ischemic stroke can be initiated by an embolic or thrombotic occlusion of a cerebral artery, and accounts for approximately 85% of all stroke cases (Gilgun-Sherki et al. 2002). Following ischemic stroke, neurons are unable to maintain their normal transmembrane ionic gradient and homoeostasis, triggering deleterious processes such as excitotoxicity, oxidative stress and inflammation, which cause neuronal and glia apoptotic and/or necrotic cell death (Khoshnam et al. 2017d; Velayatzadeh et al. 2014). A spectrum of severity is observed in the affected region of the brain, owing to differential lessening of blood supply to different zones. Thus, part of the brain tissue (core) undergoes irreversible neuronal damage due to necrotic cell death, while the surrounding tissues contain salvageable and metabolically active cells (penumbra), in which cell death occurs less rapidly (Alishahi et al. 2019; Khoshnam et al. 2017d). Salvaging of the ischemic penumbra is the main target for therapeutic agents, and may be associated with improved neurological outcomes and recovery (Aliaga et al. 2010; Kumar et al. 2010). Following cerebral ischemia a cascade of cellular and molecular events leads to ischemic damage and irretrievable cerebral injury (Moskowitz et al. 2010). The ischemic cascade is a complex series of intertwined cellular mechanisms including excitotoxicity, oxidative and nitrative stress, inflammation and apoptosis, which are deleterious for the neurons, glial and endothelial cells (Broadbent et al. 2004; Iadecola and Anrather 2011; Thangavelu et al. 2012; Vakili et al. 2011). These pathophysiological processes trigger each other in a positive feedback loop that terminates in neuronal cell death and brain damage (Velayatzadeh et al. 2014). A better understanding of the molecular and cellular mechanisms underlying stroke pathogenesis and following recovery may suggest promising and novel methods complementary to r-tPA for ischemic stroke therapy (Sun et al. 2008; Sun and Feng 2013; Sun et al. 2009).

Mechanisms of lncRNA functions

Non-coding RNAs are divided into long (>200 nt) RNAs (lncRNAs and ribosomal RNAs) and short (<200 nt) RNAs including microRNAs (miRNAs) and transfer RNAs (Mercer and Mattick 2013; Wilusz et al. 2009). LncRNAs can regulate gene expression in both transcriptional and post-transcriptional levels (Fig. 1). The mechanisms for the actions of lncRNAs at the transcriptional level include regulation and modification of chromosomes that are involved in the alteration of gene expression. Additionally, lncRNAs in post-transcriptional regulation act as competing endogenous RNAs (ceRNA) and miRNA sources, leading to RNA degradation (Bao et al. 2018).

LncRNAs may recruit different kinds of chromatin regulatory proteins in the nucleus by interacting with specific sites in the chromatin, which integrate and orchestrate the shape of the chromosome, and then suppress or activate of the genes expression, or alter the modification (acetylation or methylation) of the chromatin (Bao et al. 2018).Furthermore, lncRNAs regulate gene expression after transcription, either directly through regulating RNA splicing and RNA degradation, or indirectly by affecting miRNA functions. It has been shown that several lncRNAs have sequences base-paired to the precursor messenger RNA (pre-mRNA) and block the splicing of these pre-mRNAs, which is a crucial step for a pre-mRNA being transcribed into mRNA. LncRNAs can directly bind to mRNA and regulate the degradation of mRNA (Szcześniak and Makałowska 2016). LncRNAs can regulate gene expression by affecting the formation or function of miRNAs. Some lncRNAs contain complementary binding sites to certain miRNAs, and act as miRNA sponges, which

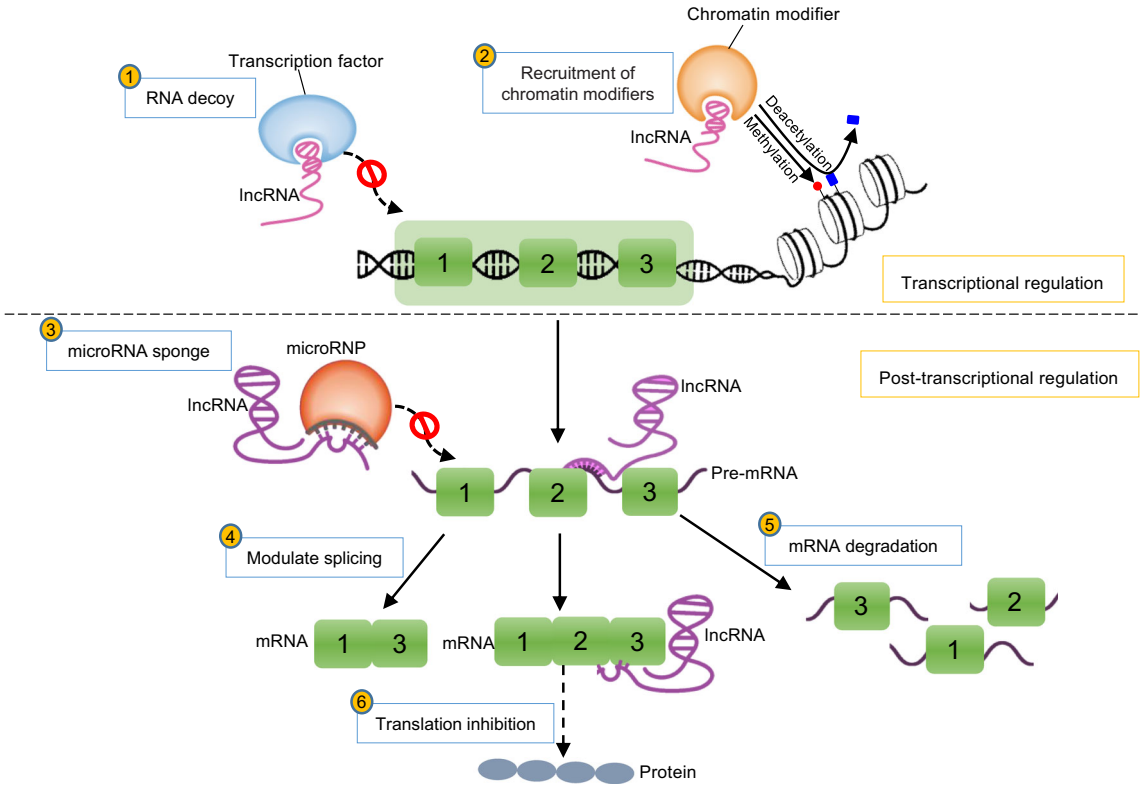

Fig. 1 Mechanisms of lncRNA function. Studies have described a range of mechanisms by which lncRNAs regulate their targets at the transcriptional and post transcriptional levels (Hu et al. 2012). (1) RNA decoys; several lncRNAs directly binding to transcription factors and titrating them away from their DNA targets (Kino et al. 2010; Ng et al. 2012). (2) Chromatin modification; lncRNAs recruits different kinds of regulatory proteins which promotes histone methylation and deacetylation on the chromatin (Bao et al. 2018). (3) MicroRNA sponge; many lncRNA genes contain embedded miRNA sequence, which soak up the target miRNA and result in the reduction of their functions in cells and titrating them away from their targets (Cesana et al. 2011; Karreth et al. 2011; Salmena et al. 2011). A few lncRNAs seem to modulate direct processing of mRNAs, including splicing (4) translation (5), and degradation (6) (Gong and Maquat 2011; Tripathi et al. 2010; Yoon et al. 2012). lncRNA, long non-coding RNA; mRNA, messenger RNA

result in the reduction of miRNA functions. Hence, lncRNAs can act as ceRNA to decrease the concentration of miRNAs in cells, and negatively regulate the functions of miRNAs (Ebert et al. 2007; Ma et al. 2014).

LncRNAs in ischemic stroke

Recently, the expression, function, and mechanisms of lncRNAs and miRNAs in ischemic stroke have drawn wide attention, and hundreds of aberrantly expressed lncRNAs were identified in ischemic patients and animal models of ischemic stroke (Dykstra-Aiello et al. 2016; Khoshnam et al. 2017b; Khoshnam et al. 2017c; Zhang et al. 2016). It has been demonstrated that several lncRNAs were up or down regulated in the cortexes of rats subjected to transient middle cerebral artery occlusion (MCAO) (Dharap et al. 2012). Recently, it has also been reported that ischemia may induce broad alteration of lncRNAs during the pathophysiology of stroke, and that they have an active role in ischemic stroke. This demonstrates their great impact on progression of cerebral ischemic injuries (Bhattarai et al. 2017).

The interplay of lncRNAs in post-stroke cell death

A microarray profiling study identifies altered lncRNA transcriptomic profiles in the brain microvascular endothelium following ischemic stroke (Zhang et al. 2016). Accumulating evidence has shown that lncRNAs play an essential role in the pathogenesis of ischemic stroke, and several lncRNAs were reported to mediate ischemia-induced apoptosis and cell death, including Malat1, Meg3, FosDT, C2dat1, N1LR and TUG1 (summarized in Fig. 2).

Metastasis associated lung adenocarcinoma transcript1 (Malat1)

Malat1 plays an important role in protecting the cerebral microvasculature against cerebral ischemia, and is one of the most highly upregulated lncRNAs after ischemic stroke (Yuan et al. 2015). Several reports demonstrated that Malat1 inhibits cancer cell apoptosis by inducing the autophagy pathways (Li et al. 2016; Yuan et al. 2016). Recent studies show that Malat1 promotes neovascularization and regulates

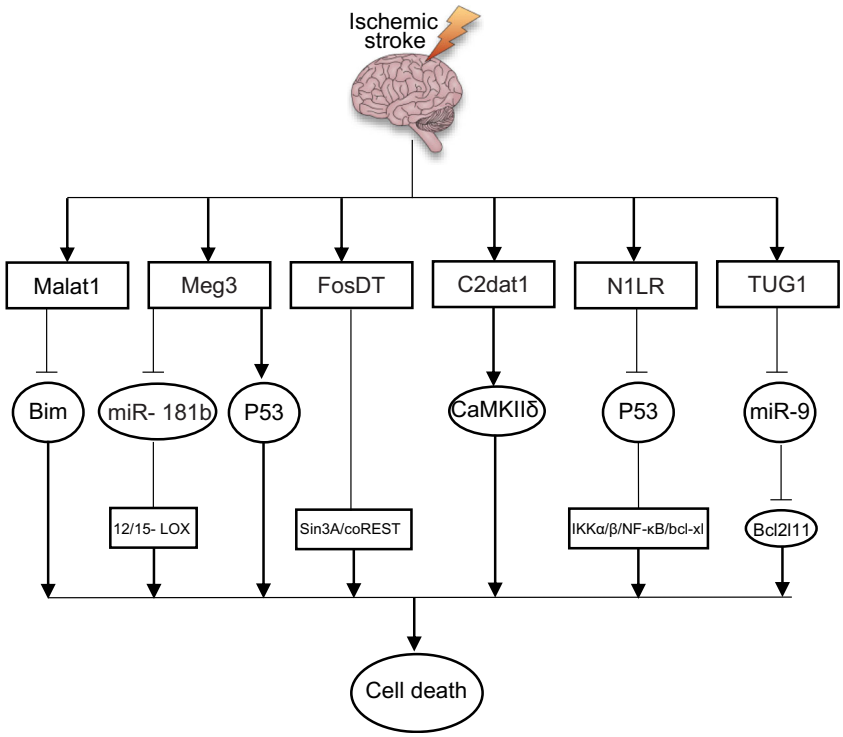

Fig. 2 Schematic of lncRNAs mediated ischemic stroke-induced cell death. Malat1; *metastasis-associate lung adenocarcinoma transcript 1,* Meg3; *maternally expressed gene 3,* FosDT; *Fos downstream transcript,* C2dat1; CaMK2D-associated transcript 1, TUG1; *taurine-upregulated gene1,* coREST; co-repressors of the transcription factor REST, NF-κB; nucleus factor kappa b, IKKα/β; IκB kinase complex, CaMKIIδ; calcium/calmodulin-dependent kinase II

endothelial cell function after hind-limb ischemia (Michalik et al. 2014).

Malat1 is identified as one of the most highly upregulated OGD (oxygen-glucose deprivation)- responsive endothelial lncRNAs (Zhang et al. 2016). Recently, a study report that Malat1 promotes brain microvascular endothelial cell (BMECs) autophagy and survival in OGD/R (Oxygen-glucose deprivation/ reoxygenation) condition, in which Malat1 served as a ceRNA by sponging miR-26b and upregulating ULK2 expression. Autophagy has been shown to have protective effects on BMECs against cerebral ischemic insults (Li et al. 2017). It has been shown that lncRNAs such as Malat1 may act as ceRNAs, namely, miRNA sponges or antagomirs, and regulate the expression of miRNA target protein (Han et al. 2015; Tang et al. 2015; Wang et al. 2016). Additionally, Malat1 plays critical protective roles in ischemic stroke, and silencing of Malat1 increased OGD-induced cell death and Caspase 3 activity in BMECs. Silencing of Malat1 also aggravated OGD-induced expression of proinflammatory cytokines such as MCP-1, IL-6, and E-selectin and increased the pro-apoptotic factor Bim in vitro. These results indicate that Malat1, by inhibiting endothelial cell death and inflammation, has protective effects against cerebral ischemic insults *(Zhang* et al. 2017*)*.

Maternally expressed gene 3 (Meg3)

Meg3 encodes a lncRNA which is widely expressed in many tissues and cells, such as brain and endothelial cells (Michalik et al. 2014; Zhou et al. 2012). Meg3 was known as a tumor suppressor lncRNA, and growing evidence shows that its expression is lost in many tumors and cancer cell lines (Mondal et al. 2015; Peng et al. 2015; Zhang et al. 2010; Zhuo et al. 2016). It has been shown that overexpression of Meg3 promotes cell apoptosis and suppresses tumor cell growth (Lu et al. 2013; Wang et al. 2012). Recently, the expression and functions of MEG3 were discovered in the nervous system and in ischemic stroke (Liu et al. 2016; Yan et al. 2016). In both OGD neurons and MCAO mice, MEG3 presents as a cytotoxic factor for ischemic injury, and its inhibition increased the neurobehavioral score and decreased the infarction and edema volume in MCAO mice (Yan et al. 2016). Meanwhile, the increase in neural cell death and apoptosis was accompanied by the increase in MEG3. Additional studies show that p53 and 12/15-LOX (12/15-Lipoxygenase) contributes to MEG3 functions. P53 plays crucial roles in DNA repair and triggering apoptosis when DNA damage proves to be irreparable (Williams and Schumacher 2016). MEG3 was found to promote the expression of the p53 gene and to facilitate neural apoptosis in ischemic stroke insulted mice. Inhibition of this association suppressed neural apoptosis and reduced infarct volume (Yan et al. 2016). 12/15-LOX is a main isoform of lipoxygenases, and it was robustly activated in the injured brain. 12/15-LOX contributing to oxidative stress-induced neuronal death following cerebral ischemia (Dharap et al. 2013; Jung et al. 2015). It has been demonstrated that production of 12/15-LOX-1 was inhibited by overexpression of miR-181b, which is a key regulator for 12/ 15-

LOX expression (Liu et al. 2016). In MCAO mice or OGD neurons, MEG3 was upregulated and acts as a ceRNA by sponging miR- 181b, which leads to upregulation of 12/15-LOX and subsequent neuronal death (Liu et al. 2016).

Fos downstream transcript (FosDT)

FosDT overlaps the Fos gene downstream (Ji et al. 2017), and its expression in rats was highly upregulated after focal ischemia in MCAO rats (Mehta et al. 2015), which contributes to post-stroke neurological dysfunction and brain damage. Inhibition of FosDT resulted in the improvment of motor function recovery and a decrease of infarct volume associated with hypoxic injuries (Mehta et al. 2015). Fos *was also found to increase following brain injury (Mehta* et al. 2015*), which is correlated with the increase in FosDT level.* In addition, Fos was found to be congenic with FosDT (Mehta et al. 2015), and may have *regulatory and/or transcriptional interactions.*

Studies have shown that FosDT binds directly to two co-repressors for the transcription factor REST (repressor element-1 silencing transcription factor), which including coREST (co-repressors of the transcription factor REST) and Sin3a (Dharap et al. 2013). REST is a repressor of synaptic transmission and neural differentiation (Paonessa et al. 2016). Evidence shows that REST and its corepressors (Sin3A and coREST) form a complex, which represses the downstream genes such as nucleus factor kappa b (NF-κB2), glutamate receptor 2(GluR2), and N-methyl-D-aspartate 1 expression, thus increasing neuronal death and brain damage following ischemic stroke (Mehta et al. 2015; Noh et al. 2012). FosDT also interacts with REST associated chromatin-modifying proteins and promotes ischemic brain injury (Mehta et al. 2015), which suggests that FosDT could be therapeutically targeted to minimize post stroke brain damage .

CaMK2D-associated transcript 1 (C2dat1)

C2dat1 was found in MCAO insulted rat brains, and its expression was accompanied by an increase in CaMK2D gene. Functionally, inhibition of C2dat1 or CaMK2D promoted cell death in the OGD/R mouse Neuro 2A (N2a) cells, and indicated possible interaction of C2dat1 with CaMK2D (Xu et al. 2016). CaMK2D mediates the intracellular Ca^{2+} signals and is highly expressed in brain and muscle tissues (Gray and Heller Brown 2014; Mattingsdal et al. 2013). In cerebral ischemia, the expression of CaMK2D was stimulated by lncRNA C2dat1, which results in an increase in the expression of CaMKIIδ (calcium/calmodulin-dependent kinase II) protein. Increasing of the CaMKIIδ protein expression induced phosphorylation of IKKα/β (IκB kinase complex), degradation of IκB (inhibitory κB), activation of NF-κB, as well as induction of anti-apoptotic protein Bcl-Xl, leading to inhibition of ischemia-induced cell apoptosis. Therefore, lncRNA C2dat1 promotes neuronal survival by upregulation of CaMKIIδ expression following cerebral ischemia (Xu et al. 2016). The family of CaMKII comprises of four isoforms (CaMKIIα, β, γ, δ) encoded by different genes (Baucum et al. 2015; Hudmon et al. 2001; Srinivasan et al. 1994). Recently, it was suggested that *CAMK2D*/CaMKIIδ and *CAMK2G*/CaMKIIγ were upregulated after acute ischemia. Overexpression of CaMKIIδ and CAMKIIγ promote neuronal survival, and their knockdown results in neuronal death after ischemia and reperfusion (I/R) (Ye et al. 2018). It was also shown that *C2dat1* and *C2dat2* were upregulated by I/R and modulate CaMKIIδ expression. OGD/R-induced CaMKIIδ expression was inhibited by knockdown of *C2dat1/2 and* decreased neuronal survival, thus proving specific targeting of *CAMK2D* by *C2dat1/2.* Mechanistically, upregulation of these CaMKII kinases led to activation of the NF-κB signaling pathway, which protects neurons from ischemic damage (Ye et al. 2018).

N1LR

LncRNA-N1LR was shown to be up-regulated in response to mild injury induced by focal I/R in both in vivo and in vitro models of ischemia (Wu et al. 2017). It was found that N1LR improved cell cycle progression and cell proliferation, and inhibited apoptosis in N2a cells subjected to OGD/R. Furthermore, N1LR lessened neuronal apoptosis and neural cell loss in I/R-induced mouse brains. Mechanistically, N1LR promoted neuroprotection possibly through prevention of the activation of p53 (Wu et al. 2017). These results revealed that N1LR may be essential for the neurons to resist ischemic damage. Interestingly, it was demonstrated that N1LR overlaps with the 5′- UTR of the protein-coding gene Nck1. It is thought that Nck1 is involved in cellular remodeling, glucose tolerance, and insulin signaling. Its activity increases after cerebral ischemia. Nck1 expression is increased by knockdown of N1LR. However, expression of Nck1 is not affected by overexpression of N1LR. Therefore, the mechanism by which N1LR interacts with Nck1 is still unclear in ischemic stroke (Wu et al. 2017).

Taurine-upregulated gene 1 (TUG1)

TUG1 was initially detected in taurine-treated mouse retinal cells and is important for retinal development (Young et al. 2005). TUG1 regulates the methylation of H3K27me3 to repress gene expression (Conway et al. 2015), and also acted as a sponge for miRNAs such as miR-9, miR-144, miR-26a, miR-377, miR-300, miR-335, and miR-299 (Cai et al. 2017; Chen et al. 2017; Duan et al. 2017; Ji et al. 2016; Khalil et al. 2009; Ma et al. 2017; Wang et al. 2017). It has been shown that expression of TUG1 was upregulated in brain ischemic penumbra of the MCAO model, and similar results were observed in cultured neurons following OGD insult.

Knockdown of TUG1 promoted cell survival and decreased the ratio of apoptotic cells, which may be regulated by decreasing the Bcl2l11 protein and increasing miRNA-9 expression (Chen et al. 2017). MiR-9 is highly expressed in neurogenic regions (Brunkow and Tilghman 1991), and inhibits bcl2l11, which is a pro-apoptosis protein in ischemic injury. Therefore, TUG1 exerts its functions by sponging up miR-9, and subsequently weakens the inhibitory effects of miR- 9 on Bcl2l11, leading to a cytotoxic effect under ischemic conditions (Chen et al. 2017). Recent finding showed that TUG1, which could be as a miR-145a-5p sponge, is required for the release of inflammatory cytokines and microglial activation after OGD (Wang et al. 2019).

Future perspectives and challenges

Several studies have reported that certain lncRNAs play a critical role in cell death during ischemic stroke (Dykstra-Aiello et al. 2016). Studies on the regulatory mechanisms of lncRNAs in experimental stroke models may provide a promising therapeutic target for ischemic stroke patients (Zhang et al. 2018).

Along with intensive studies, the exploration of lncRNAs still faces multiple challenges. First, the complexity of lncRNAs' diverse functions hamper the study of their molecular mechanisms, and current studies on identifying their diverse functions and mechanisms have been relatively small-scale to date. More independent studies may help validate the results and drive reliable conclusions, but there is still a long way to go before this knowledge can be applied to the clinic (Zhang et al. 2018). Second, most lncRNAs are less reliable as therapeutic targets in ischemic stroke patients, owing their rapid degradation by the abundant RNases of the cells. Despite the challenges, lncRNA-based therapeutics offer promising strategies to decrease neuronal apoptosis and cell death following ischemic stroke. Many studies remain to be performed in order to identify candidate lncRNAs, to design chemical modifications or formulations for better delivery of lncRNAs, to better understand how lncRNAs exert their effects via hundreds of targets, and to find methods to moderate unwanted side effects (Zhang et al. 2018). Clinically effective lncRNA-based drugs and successful clinical trials will certainly advance our fight against ischemic stroke-induced cell death.

Conclusion

Taken together, lncRNAs play important roles in ischemic stroke-induced cell death. Studies to elucidate the functions and mechanisms of lncRNAs have increased in recent years, and several lncRNAs were reported to be associated with ischemic stroke pathogenesis (Boon et al. 2016). The bulk of aberrantly expressed lncRNAs were found in the brain of in vivo and in vitro ischemic insulted models (Dharap et al. 2012; Zhang et al. 2016; Zhao et al. 2015), which provides a unique view of the pathobiology of ischemic stroke. In recent years, great progress has been made to uncover the potential roles of lncRNAs in ischemic stroke. Elucidating the mechanisms and functions of the lncRNAs under ischemic conditions may lead to potential opportunities for identifying biomarkers and novel therapeutic targets of ischemic stroke. LncRNAs may act as biomarkers, therapeutic target, or a novel epigenetic intervention tool for decreasing and prevention of cell death in ischemic stroke insulted patients. Further, lncRNAs may provide a better understanding of pathophysiological process underlying cell death following ischemic stroke. However, this field is still facing a lot of challenges. Till now, only a very small number of lncRNAs have been studied in the ischemic stroke. With advances in our understanding about expression and function of lncRNAs in the pathogenesis of ischemic stroke, we can expect to identify new biomarkers and therapeutic targets for the treatment and prevention of cell death following ischemic stroke. Their growing efficacy and accuracy will be of benefit to ischemic stroke patients.

References

Aliaga E, Silhol M, Bonneau N, Maurice T, Arancibia S, Tapia-Arancibia L (2010) Dual response of BDNF to sublethal concentrations of β-amyloid peptides in cultured cortical neurons. Neurobiol Dis 37: 208–217

Alishahi M, Farzaneh M, Ghaedrahmati F, Nejabatdoust A, Sarkaki A, Khoshnam SE (2019) NLRP3 inflammasome in ischemic stroke: as possible therapeutic target. Int J Stroke 1747493019841242

Bao M-H, Szeto V, Yang BB, Zhu S-z, Sun H-S, Feng Z-P (2018) Long non-coding RNAs in ischemic stroke. Cell Death Dis 9:281

Baucum AJ, Shonesy BC, Rose KL, Colbran RJ (2015) Quantitative proteomics analysis of CaMKII phosphorylation and the CaMKII interactome in the mouse forebrain. ACS Chem Neurosci 6:615–631

Bhattarai S, Pontarelli F, Prendergast E, Dharap A (2017) Discovery of novel stroke-responsive lncRNAs in the mouse cortex using genome-wide. RNA-seq. Neurobiol Dis 108:204–212

Boon RA, Jaé N, Holdt L, Dimmeler S (2016) Long noncoding RNAs: from clinical genetics to therapeutic targets? J Am Coll Cardiol 67: 1214–1226

Broadbent NJ, Squire LR, Clark RE (2004) Spatial memory, recognition memory, and the hippocampus. Proc Natl Acad Sci U S A 101: 14515–14520

Brunkow ME, Tilghman S (1991) Ectopic expression of the H19 gene in mice causes prenatal lethality. Genes Dev 5:1092–1101

Cai H et al (2017) Long non-coding RNA taurine upregulated 1 enhances tumor-induced angiogenesis through inhibiting microRNA-299 in human glioblastoma. Oncogene 36:318

Carpenter S et al (2013) A long noncoding RNA mediates both activation and repression of immune response genes. science 341:789–792

Cesana M et al (2011) A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous. RNA. Cell 147: 358–369

Chen S et al (2017) LncRNA TUG1 sponges microRNA-9 to promote neurons apoptosis by up-regulated Bcl2l11 under ischemia. Biochem Biophys Res Commun 485:167–173

Conway E, Healy E, Bracken AP (2015) PRC2 mediated H3K27 methylations in cellular identity and cancer. Curr Opin Cell Biol 37:42–48

Dharap A, Nakka VP, Vemuganti R (2012) Effect of focal ischemia on long noncoding RNAs. Stroke 43:2800–2802

Dharap A, Pokrzywa C, Vemuganti R (2013) Increased binding of stroke-induced long non-coding RNAs to the transcriptional corepressors Sin3A and coREST. ASN Neuro 5:AN20130029

Donkor ES (2018) Stroke in the century: a snapshot of the burden, epidemiology, and quality of life stroke research and treatment 2018

Duan L-J, Ding M, Hou L-J, Cui Y-T, Li C-J, Yu D-M (2017) Long noncoding RNA TUG1 alleviates extracellular matrix accumulation via mediating microRNA-377 targeting of PPARγ in diabetic nephropathy. Biochem Biophys Res Commun 484:598–604

Dykstra-Aiello C et al (2016) Altered expression of long noncoding RNAs in blood after ischemic stroke and proximity to putative stroke risk loci. Stroke 47:2896–2903

Ebert MS, Neilson JR, Sharp PA (2007) MicroRNA sponges: competitive inhibitors of small RNAs in mammalian cells. Nat Methods 4:721

Feigin VL, Norrving B, Mensah GA (2017) Global burden of stroke. Circ Res 120:439–448

Gilgun-Sherki Y, Rosenbaum Z, Melamed E, Offen D (2002) Antioxidant therapy in acute central nervous system injury: current state. Pharmacol Rev 54:271–284

Gong C, Maquat LE (2011) lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3′ UTRs via Alu elements. Nature 470:284

Gray CBB, Heller Brown J (2014) CaMKIIdelta subtypes: localization and function. Front Pharmacol 5:15

Group I-C (2012) The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 379:2352–2363

Han X, Yang F, Cao H, Liang Z (2015) Malat1 regulates serum response factor through miR-133 as a competing endogenous RNA in myogenesis. FASEB J 29:3054–3064

Hawkins KE et al (2017) Targeting resolution of neuroinflammation after ischemic stroke with a lipoxin A4 analog: protective mechanisms and long-term effects on neurological recovery. Brain and behavior 7:e00688

Hu W, Alvarez-Dominguez JR, Lodish HF (2012) Regulation of mammalian cell differentiation by long non-coding RNAs. EMBO Rep 13:971–983

Huang H-L, Lin C-C, Jeng K-CG, Yao P-W, Chuang L-T, Kuo S-L, Hou C-W (2012) Fresh green tea and gallic acid ameliorate oxidative stress in kainic acid-induced status epilepticus. J Agric Food Chem 60:2328–2336

Hudmon A, Kim SA, Kolb SJ, Stoops JK, Waxham MN (2001) Light scattering and transmission electron microscopy studies reveal a mechanism for calcium/calmodulin-dependent protein kinase II self-association. J Neurochem 76:1364–1375

Iadecola C, Anrather J (2011) The immunology of stroke: from mechanisms to translation. Nat Med 17:796

Ji T-T, Huang X, Jin J, Pan S-H, Zhuge X-J (2016) Inhibition of long non-coding RNA TUG1 on gastric cancer cell transference and invasion through regulating and controlling the expression of miR-144/c-met axis. Asian Pac J Trop Med 9:508–512

Ji Y, Guo X, Zhang Z, Huang Z, Zhu J, Chen Q-H, Gui L (2017) CaMKIIδ meditates phenylephrine induced cardiomyocyte hypertrophy through store-operated Ca2+ entry. Cardiovasc Pathol 27:9–17

Jung JE, Karatas H, Liu Y, Yalcin A, Montaner J, Lo EH, Van Leyen K (2015) STAT-dependent upregulation of 12/15-lipoxygenase contributes to neuronal injury after stroke. J Cereb Blood Flow Metab 35:2043–2051

Karreth FA et al (2011) In vivo identification of tumor-suppressive PTEN ceRNAs in an oncogenic BRAF-induced mouse model of melanoma. Cell 147:382–395

Khalil AM et al (2009) Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc Natl Acad Sci 106:11667–11672

Khoshnam SE, Sarkaki A, Khorsandi L, Winlow W, Badavi M, Moghaddam HF, Farbooda Y (2017a) Vanillic acid attenuates effects of transient bilateral common carotid occlusion and reperfusion in rats. Biomed Pharmacother 96:667–674

Khoshnam SE, Winlow W, Farbood Y, Moghaddam HF, Farzaneh M (2017b) Emerging roles of microRNAs in ischemic stroke: as possible therapeutic agents. J Stroke 19:166

Khoshnam SE, Winlow W, Farzaneh M (2017c) The interplay of MicroRNAs in the inflammatory mechanisms following ischemic stroke. J Neuropathol Exp Neurol 76:548–561

Khoshnam SE, Winlow W, Farzaneh M, Farbood Y, Moghaddam HF (2017d) Pathogenic mechanisms following ischemic stroke. Neurol Sci 38:1167–1186

Khoshnam SE, Farbood Y, Moghaddam HF, Sarkaki A, Badavi M, Khorsandi L (2018a) Vanillic acid attenuates cerebral hyperemia, blood-brain barrier disruption and anxiety-like behaviors in rats following transient bilateral common carotid occlusion and reperfusion. Metab Brain Dis:1–9

Khoshnam SE, Sarkaki A, Rashno M, Farbood Y (2018b) Memory deficits and hippocampal inflammation in cerebral hypoperfusion and reperfusion in male rats: Neuroprotective role of vanillic acid Life sciences

Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP (2010) Noncoding RNA gas5 is a growth arrest–and starvation-associated repressor of the glucocorticoid receptor. Sci Signal 3:ra8

Kumar G, Goyal MK, Sahota PK, Jain R (2010) Penumbra, the basis of neuroimaging in acute stroke treatment: current evidence. J Neurol Sci 288:13–24

Li L et al. (2016) Long noncoding RNA MALAT1 promotes aggressive pancreatic cancer proliferation and metastasis via the stimulation of autophagy. Mol Cancer Ther

Li Z, Li J, Tang N (2017) Long noncoding RNA Malat1 is a potent autophagy inducer protecting brain microvascular endothelial cells against oxygen-glucose deprivation/reoxygenation-induced injury by sponging miR-26b and upregulating ULK2 expression. Neuroscience 354:1–10

Liu X, Hou L, Huang W, Gao Y, Lv X, Tang J (2016) The mechanism of long non-coding RNA MEG3 for neurons apoptosis caused by hypoxia: mediated by miR-181b-12/15-LOX signaling pathway. Front Cell Neurosci 10:201

Lorenzen JM, Martino F, Thum T (2012) Epigenetic modifications in cardiovascular disease. Basic Res Cardiol 107:245

Lu K-h et al (2013) Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer 13:461

Ma X, Shao C, Jin Y, Wang H, Meng Y (2014) Long non-coding RNAs: a novel endogenous source for the generation of dicer-like 1-dependent small RNAs in Arabidopsis thaliana. RNA Biol 11:373–390

Ma F, Wang S-h, Cai Q, L-y J, Zhou D, Ding J, Z-w Q (2017) Long non-coding RNA TUG1 promotes cell proliferation and metastasis by negatively regulating miR-300 in gallbladder carcinoma. Biomed Pharmacother 88:863–869

Mattingsdal M et al (2013) Pathway analysis of genetic markers associated with a functional MRI faces paradigm implicates polymorphisms in calcium responsive pathways. Neuroimage 70:143–149
Mehta SL, Kim T, Vemuganti R (2015) Long noncoding RNA FosDT promotes ischemic brain injury by interacting with REST-associated chromatin-modifying proteins. J Neurosci 35:16443–16449
Mercer TR, Mattick JS (2013) Structure and function of long noncoding RNAs in epigenetic regulation. Nat Struct Mol Biol 20:300
Mercer TR, Dinger ME, Mattick JS (2009) Long non-coding RNAs: insights into functions. Nat Rev Genet 10:155
Michalik KM et al (2014) Long noncoding RNA MALAT1 regulates endothelial cell function and vessel growth. Circ Res 114:1389–1397
Mondal T et al (2015) MEG3 long noncoding RNA regulates the TGF-β pathway genes through formation of RNA–DNA triplex structures. Nat Commun 6:7743
Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G (2013) The epidemiology of cardiovascular diseases in sub-Saharan Africa: the global burden of diseases, injuries and risk factors 2010 study. Prog Cardiovasc Dis 56:234–239
Moskowitz MA, Lo EH, Iadecola C (2010) The science of stroke: mechanisms in search of treatments. Neuron 67:181–198
Ng SY, Johnson R, Stanton LW (2012) Human long non-coding RNAs promote pluripotency and neuronal differentiation by association with chromatin modifiers and transcription factors. EMBO J 31:522–533
Noh K-M et al (2012) Repressor element-1 silencing transcription factor (REST)-dependent epigenetic remodeling is critical to ischemia-induced neuronal death. Proc Natl Acad Sci:201121568
Paonessa F et al (2016) Regulation of neural gene transcription by optogenetic inhibition of the RE1-silencing transcription factor. Proc Natl Acad Sci 113:E91–E100
Peng W et al (2015) Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression. J Exp Clin Cancer Res 34:79
Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP (2011) A ceRNA hypothesis: the Rosetta stone of a hidden RNA language? Cell 146:353–358
Schaukowitch K, Kim T-K (2014) Emerging epigenetic mechanisms of long non-coding RNAs. Neuroscience 264:25–38
Srinivasan M, Edman CF, Schulman H (1994) Alternative splicing introduces a nuclear localization signal that targets multifunctional CaM kinase to the nucleus. J Cell Biol 126:839–852
Sun H-s, Feng Z-p (2013) Neuroprotective role of ATP-sensitive potassium channels in cerebral ischemia. Acta Pharmacol Sin 34:24
Sun H-S et al (2008) Effectiveness of PSD95 inhibitors in permanent and transient focal ischemia in the rat. Stroke 39:2544–2553
Sun H-S et al (2009) Suppression of hippocampal TRPM7 protein prevents delayed neuronal death in brain ischemia. Nat Neurosci 12:1300
Sun H-S et al (2015) Neuronal KATP channels mediate hypoxic preconditioning and reduce subsequent neonatal hypoxic–ischemic brain injury. Exp Neurol 263:161–171
Szcześniak MW, Makałowska I (2016) lncRNA-RNA interactions across the human transcriptome. PLoS One 11:e0150353
Tan Z et al (2014) Combination treatment of r-tPA and an optimized human apyrase reduces mortality rate and hemorrhagic transformation 6 h after ischemic stroke in aged female rats. Eur J Pharmacol 738:368–373
Tang Y, Jin X, Xiang Y, Chen Y, Shen C-x, Zhang Y-c, Li Y-g (2015) The lncRNA MALAT1 protects the endothelium against ox-LDL-induced dysfunction via upregulating the expression of the miR-22-3p target genes CXCR2 and AKT. FEBS Lett 589:3189–3196
Tekle WG et al (2012) Intravenous thrombolysis in expanded time window (3-4.5 hours) in general practice with concurrent availability of endovascular treatment. J Vasc Interv Neurol 5:22
Thangavelu K, Kannan R, Kumar NS, Rethish E, Sabitha S, Sayeeganesh N (2012) Significance of localization of mandibular foramen in an inferior alveolar nerve block. J Nat Sci Biol Med 3:156
Tripathi V et al (2010) The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 39:925–938
Vakili A, Mojarrad S, Akhavan MM, Rashidy-Pour A (2011) Pentoxifylline attenuates TNF-α protein levels and brain edema following temporary focal cerebral ischemia in rats. Brain Res 1377:119–125
Van der Worp H et al (2002) The effect of tirilazad mesylate on infarct volume of patients with acute ischemic stroke. Neurology 58:133–135
Velayatzadeh M, ASKARY SA, Beheshti M, Mahjob S, Hoseini M (2014) Measurement of heavy metals (HG, CD, SN, ZN, NI, FE) in canned tuna fish product in central cities, Iran
Wang P, Ren Z, Sun P (2012) Overexpression of the long non-coding RNA MEG3 impairs in vitro glioma cell proliferation. J Cell Biochem 113:1868–1874
Wang SH et al (2016) The lnc RNA MALAT 1 functions as a competing endogenous RNA to regulate MCL-1 expression by sponging miR-363-3p in gallbladder cancer. J Cell Mol Med 20:2299–2308
Wang Y, Yang T, Zhang Z, Lu M, Zhao W, Zeng X, Zhang W (2017) Long non-coding RNA TUG 1 promotes migration and invasion by acting as a ce RNA of miR-335-5p in osteosarcoma cells. Cancer Sci 108:859–867
Wang H, Liao S, Yu J (2019) Abstract WP347: long non-coding RNA TUG1 contributes to microglial activation after oxygen glucose deprivation stroke 50:AWP347-AWP347
Williams AB, Schumacher B (2016) p53 in the DNA-damage-repair process. Cold Spring Harbor perspectives in medicine a026070
Wilusz JE, Sunwoo H, Spector DL (2009) Long noncoding RNAs: functional surprises from the RNA world. Genes Dev 23:1494–1504
Wu Z et al (2017) LncRNA-N1LR enhances neuroprotection against ischemic stroke probably by inhibiting p53 phosphorylation. Mol Neurobiol 54:7670–7685
Xiao H et al (2015) LncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging miR-200s in clear cell kidney carcinoma. Oncotarget 6:38005
Xu Q et al (2016) Long non-coding RNA C2dat1 regulates CaMKIIδ expression to promote neuronal survival through the NF-κB signaling pathway following cerebral ischemia. Cell Death Dis 7:e2173
Yan H, Yuan J, Gao L, Rao J, Hu J (2016) Long noncoding RNA MEG3 activation of p53 mediates ischemic neuronal death in stroke. Neuroscience 337:191–199
Yang F, Bi J, Xue X, Zheng L, Zhi K, Hua J, Fang G (2012) Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. FEBS J 279:3159–3165
Ye J et al. (2018) Ischemic injury-induced CaMKIIδ and CaMKIIγ confer neuroprotection through the NF-κB signaling pathway. Mol Neurobiol 1–14
Yoon J-H et al (2012) LincRNA-p21 suppresses target mRNA translation. Mol Cell 47:648–655
Young T, Matsuda T, Cepko C (2005) The noncoding RNA taurine upregulated gene 1 is required for differentiation of the murine retina. Curr Biol 15:501–512
Yu G, Wu F, Wang E-S (2015) BQ-869, a novel NMDA receptor antagonist, protects against excitotoxicity and attenuates cerebral ischemic injury in stroke. Int J Clin Exp Pathol 8:1213
Yuan L, Zhang J, Chen YE, Yin K-J (2015) Long non-coding RNAs mediate cerebrovascular endothelial pathologies in ischemic stroke. Stroke 46:A72–A72
Yuan P, Cao W, Zang Q, Li G, Guo X, Fan J (2016) The HIF-2α-MALAT1-miR-216b axis regulates multi-drug resistance of hepatocellular carcinoma cells via modulating autophagy. Biochem Biophys Res Commun 478:1067–1073

Zhang X et al. (2010) Maternally expressed gene 3, an imprinted non-coding RNA gene, is associated with meningioma pathogenesis and progression. Cancer research:0008-5472. CAN-0009-3885

Zhang J et al (2016) Altered long non-coding RNA transcriptomic profiles in brain microvascular endothelium after cerebral ischemia. Exp Neurol 277:162–170

Zhang X, Tang X, Liu K, Hamblin MH, Yin K-J (2017) Long non-coding RNA Malat1 regulates cerebrovascular pathologies in ischemic stroke. J Neurosci:3389–3316

Zhang X, Hamblin MH, Yin K-J (2018) Noncoding RNAs and stroke the neuroscientist 1073858418769556

Zhao F et al (2015) Microarray profiling and co-expression network analysis of LncRNAs and mRNAs in neonatal rats following hypoxic-ischemic brain damage. Sci Rep 5:13850

Zhou Y, Zhang X, Klibanski A (2012) MEG3 non-coding RNA: a tumor suppressor. J Mol Endocrinol: JME-12-0008

Zhuo H et al (2016) The aberrant expression of MEG3 regulated by UHRF1 predicts the prognosis of hepatocellular carcinoma. Mol Carcinog 55:209–219