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Non-coding RNAs: The potential biomarker or therapeutic target in hepatic ischemia-reperfusion injury

Shao JL *et al.* ncRNAs in HIRI

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Abstract

Hepatic ischemia-reperfusion injury (HIRI) is the major complication of liver surgery and liver transplantation, that may increase the postoperative morbidity, mortality, tumor progression, and metastasis. The underlying mechanisms have been extensively investigated in recent years. Among these, oxidative stress, inflammatory responses, immunoreactions, and cell death are the most studied. Non-coding RNAs (ncRNAs) are defined as the RNAs that do not encode proteins, but can regulate gene expressions. In recent years, ncRNAs have emerged as research hotspot for various diseases. During the progression of HIRI, ncRNAs are differentially expressed, while these dysregulations of ncRNAs, in turn, have been verified to be related to the above pathological processes involved in HIRI. ncRNAs mainly contain microRNAs, long ncRNAs, and circular RNAs, some of which have been reported as biomarkers for early diagnosis or assessment of liver damage severity, and as therapeutic targets to attenuate HIRI. Here, we briefly summarize the common pathophysiology of HIRI, describe the current knowledge of ncRNAs involved in HIRI in animal and human studies, and discuss the potential of ncRNA-targeted therapeutic strategies. Given the scarcity of clinical trials, there is still a long way to go from pre-clinical to clinical application, and further studies are needed to uncover their potential as therapeutic targets.

Key Words: Hepatic ischemia-reperfusion injury; Non-coding RNAs; MicroRNAs; Long non-coding RNAs; Circular RNAs

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Core Tip: This review focuses on the recent progress in understanding non-coding RNAs (ncRNAs) in hepatic ischemia-reperfusion injury (HIRI). HIRI can alter ncRNAs expressions, which in turn modulates the pathophysiological processes that contribute to

the development of HIRI. Differentially expressed ncRNAs from different sources (the liver tissues, serums and cells) are involved in oxidative stress, inflammatory responses, cell death and so on. ncRNAs are regarded as biomarkers for the diagnosis and assessment of liver damage severity, or as therapeutic targets for HIRI; however, their clinical transformation will still take a long time.

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INTRODUCTION

Hepatic ischemia-reperfusion injury (HIRI) is a common clinical issue that occurs during major liver resection, liver transplantation, and liver trauma^[1-3]. HIRI usually causes liver injury, early transplantation failure, liver failure and even multiple-organ failure. Although existing studies have shown that several signaling pathways, such as oxidative stress, inflammatory response, and cell death, participate in the pathological process of HIRI^[4-6], current treatments and pharmacological approaches cannot completely address this problem. Therefore, much more new molecules need to be explored for the diagnosis and treatment of HIRI.

Non-coding RNAs (ncRNAs) are a cluster of functional RNAs that cannot encode protein^[7,8]. In recent years, ncRNAs have become a hot area of research and have been reported to play a significant role in various diseases, including cancers, nervous system diseases, and ischemia/reperfusion injuries^[9-11]. ncRNAs mainly consist of microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), which have been shown to modulate genes expression, and participate in many critical biological processes at different levels (*e.g.* immune responses, oxidative stress reactions, apoptosis, autophagy, and energy metabolism)^[12-14]. The role of ncRNAs in HIRI is explored in a few studies, and has attracted the attention of many researchers.

ncRNAs are regarded as potential biomarkers or therapeutic targets for assessing or attenuating HIRI development. As the present studies are mainly in the preclinical stage, and clinical investigations are lacking, there are still large research prospects for the diagnosis, prevention, and treatment of HIRI. This review briefly illustrates the well-

studied molecular mechanisms of HIRI and summarizes the relevant ncRNAs and their roles in the pathological process of HIRI to provide a reference for further research.

HIRI AND THE UNDERLYING MECHANISMS

HIRI is usually classified into two types, warm IRI *in situ* and cold IRI *in vitro*, and the cells involved are different. Warm IRI is characterized by hepatocellular injury, which is mainly caused by Kupffer cells (KCs) induced oxidative stress and neutrophils recruitment^[15]. Cold IRI is associated with sinusoidal endothelial cells (SECs) damage^[11]. Although the initial cells are different, they do share common subsequent reactions: activation of cell death programs such as apoptosis, necrosis, pyroptosis, and autophagy, thus contributing to the development of inflammation^[1,16-18].

The mechanisms involved in HIRI pathogenesis are multifactorial and complex. Numerous studies have demonstrated several molecular mechanisms that contribute to the development of HIRI^[19], such as anaerobic metabolism, immune response^[20], microcirculatory dysfunction^[21], and gene transcription^[6,21].

Oxidative stress

The most widely studied mechanism is oxidative stress, which is defined as an imbalance between the oxidant and antioxidant systems, resulting in tissue damages^[22,23]. For instance, CeO₂, NO, and chlorogenic acid have a liver-protective effect by reducing oxidative stress during HIRI^[20,24,25]. In contrast, Han *et al*^[26] found that hyperglycemia aggravates HIRI by inducing reactive oxygen species (ROS) mediated oxidative stress. ROS are the most critical reactive molecules involved in HIRI. Enormous amounts of ROS are usually generated by mitochondria and KCs during reperfusion, which can result in apoptosis, autophagy, inflammation, protein and DNA damage, and worsened hepatocyte injury^[5,22]. Prussian blue scavenger is a potential therapeutic agent for treating HIRI with ROS-scavenging and anti-inflammatory properties^[27]. OX40 expression in neutrophils can increase ROS production, which in turn activates neutrophils and, aggravates HIRI^[28]. Dugbartey *et al*^[29] designed a reversible redox probe REPOM to

monitor ROS during HIRI for early diagnosis and timely intervention. Furthermore, an increasing number of studies on gene therapy for oxidative stress have attracted the attention of researchers in recent years. Therefore, strategies that are aimed at inhibiting oxidative stress or scavenging ROS may alleviate HIRI, and novel antioxidant regulatory molecules are required.

Inflammatory response and immune response

The inflammatory response is another major mechanism underlying HIRI. During HIRI development, KCs and SECs are initially activated^[30,31], and generate a range of inflammatory mediators including cytokines, such as PAF, TNF α , and interleukins (e.g., IL-1, IL-6, IL-12, and IL-23), which could lead to the inflammatory response involved in HIRI development^[32-34]. In addition, several cytokines (e.g., PAF, leukotriene B4, IL-8, and IL-17) induce neutrophil accumulation, which plays a role in the process of HIRI^[35]. Furthermore, activated neutrophils can form neutrophil extracellular traps (NETs) *via* TLR-dependent pathways, that initiate inflammatory responses during HIRI^[36]. This local inflammatory state can cause a systemic inflammatory response, leading to systemic inflammatory response syndrome and even multiple-organ failures.

Both innate and adaptive immune responses play important roles in HIRI^[37,38]. KCs can increase the production of damage-associated molecular patterns (DAMPs), such as ATP, histones, high mobility group box 1 (HMGB1), S100, and heat shock proteins, which are released into the circulation and induce cytokine/chemokine storms to attract neutrophils and other immune cells^[39]. In contrast, DAMPs can bind to Toll-like receptors (TLRs) and drive immune responses. Targeting the DAMP pathways alleviates HIRI. For example, HMGB1/NLRP3 inflammasome inhibition attenuated HIRI^[40]. In addition, the complement system serves as an important contributor to the process of HIRI^[41-43]. Therefore, targeting inflammation-oriented therapies may alleviate HIRI.

Cell death

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Cell death is a stable pathological indicator of I/R injury, including apoptosis, necrosis, autophagy, pyroptosis, and ferroptosis. Among them, apoptosis, necrosis, and autophagy are the most common types of cell death during HIRI and may share the same stimuli and signaling pathways^[44]. For example, hydrogen sulfide (H₂S) effectively alleviates HIRI by attenuating hepatocyte apoptosis *via* inhibition of the endoplasmic reticulum (ER) stress response^[22]. Eucommia ulmoides polysaccharide administration notably reduced the area of liver necrosis in a rat HIRI model^[45]. Cafestol preconditioning can inhibit apoptosis and autophagy in hepatocytes, thus attenuating HIRI, by suppressing the extracellular signal-regulated/erxisome proliferator-activated receptor gamma (ERK/PPAR γ) pathway^[46]. Moreover, some studies suggest that mitochondrial autophagy is a key pathological mechanism underlying age-dependent hypersensitivity to HIRI^[16]. In our previous studies, we found that octreotide pretreatment mitigated HIRI and attenuated kidney injury caused by HIRI by inhibiting hepatocellular apoptosis and enhancing autophagy^[47-49]. These three processes usually coexist and participate in the development of HIRI.

The role of pyroptosis in HIRI remains unclear. Pyroptosis is a form of regulated cell death driven by perturbations in extracellular or intracellular homeostasis related to innate immunity. It is usually associated with IL-1 β and IL-18 secretion and hence mediates robust pro-inflammatory effects^[50]. Adipose-derived mesenchymal stem cells reduce pyroptosis in HIRI by inhibiting the NF- κ B pathway and activating the Wnt/ β -catenin pathway^[51,52]. In the hepatic tissue of HIRI mice, lncRNA KCNQ1OT1 increased, which modulated miR-142a-3p/HMGB1, thereby promoting pyroptosis^[15]. Under HIRI condition, IKZF1 increased, but sirtuin 1 (SIRT1) decreased in both human and mouse livers. Further investigation indicated that IKZF1 augmented pyroptosis through negatively regulating SIRT1 expression. Hence, pyroptosis plays an important role in the development of HIRI, and targeting pyroptosis is a promising approach for attenuating HIRI. However, the role of pyroptosis in HIRI requires further investigations.

In addition to the common types of cell death, ferroptosis has recently been reported to participate in HIRI. In 2012, Dixon *et al*^[53] first proposed the definition of ferroptosis,

which is characterized by the iron-dependent accumulation of lethal lipid ROS. Then ferroptosis was proved contributed to HIRI pathogenesis. Deferoxamine, (an iron chelator) attenuated HIRI and lipid peroxidation, whereas iron overload was a novel risk factor for HIRI^[53]. Bioinformatics analysis was conducted to predict the genes related to ferroptosis in HIRI. Five genes (ATF3, IL6, IL1B, CDKN1A, and PTGS2) and several miRNAs (miR-128-3p and miR-24-3p) were identified^[54]. Subsequently, Maresin conjugate in tissue regeneration 1 ameliorated ferroptosis-induced HIRI by promoting nuclear factor erythroid-derived 2-like 2 expression^[55]. However, μ opioid receptor alleviated ferroptosis in HIRI *via* the HIF-1 α / axis^[56]. These results indicate that ferroptosis plays a critical role in HIRI.

Other mechanisms

Many other regulatory mechanisms, in addition to those mentioned in previous sections, are involved in the progress of HIRI. For instance, mitochondrial dysfunction (such as mitophagy and impairment of mitochondrial permeability) plays a vital role in HIRI^[16]. Acidic microenvironment has been reported to be a key factor affecting HIRI through the regulation of PPAR- γ ^[26]. Besides, lipid metabolites^[57,58], calcium overload^[56], adenosine triphosphate depletion^[55], gap junctions^[6], dysfunctional microcirculation^[5,53], and endoplasmic reticulum stress^[26,29] can affect the development of HIRI.

MIRNAS

miRNAs are a class of endogenous single-chain, small ncRNAs with (21-25 nucleotides in length). ² The first known miRNAs (lin-4 and let-7) were identified in *C. elegans* in 1993^[59]. Subsequently, more miRNAs have been found in plants, viruses, and animals. miRNAs produced from hairpin-like precursor transcripts are regulators of posttranscriptional and transcriptional gene expression^[7,60], and are involved in various biological processes, such as development, apoptosis, metabolism, and proliferation^[61]. miRNAs play important roles in human diseases, such as cancer, cardiovascular diseases,

and genetic diseases^[62,63]. In HIRI, numerous miRNAs have been thus far identified as biomarkers or therapeutic targets in the past decades (shown in Table 1).

In 2009, Xu *et al*^[64] reported for the first time that under the criteria of fold change > 2 and P value < 0.5 , 78 miRNAs (40 down-regulated/38 up-regulated) were identified in the liver upon I/R injury. Among them, four miRNAs (miR-23a, miR-326, miR-346_MM1, and miR-370) were significantly downregulated by ischemic preconditioning (IPC) compared to non-preconditioned controls, implying a potential role of these miRNAs in the protective mechanism of IPC against hepatic injury^[64]. Subsequently, more miRNAs were identified and their specific regulatory mechanisms were reported. The rise or fall of miRNAs determines their modulatory effects on HIRI development, and the different target genes of miRNAs allow them to be involved in the different mechanisms underlying HIRI, such as inflammation, apoptosis, and oxidative stress. The relevant information is presented in Tables 1 and 2.

miR-34

During HIRI, miR-34 is upregulated and mediates several important signaling pathways involved in various biological processes, such as inflammatory responses and apoptosis. Carbon monoxide (CO) inhalation or p-coumaric acid reduces miR-34a expression in the liver tissue, thus increasing SIRT1, which in turn mitigates HIRI by alleviating inflammatory responses, hepatocellular apoptosis and autophagy^[64,65]. Similarly, H₂S and crocin exerted hepatoprotective effects in a rat model of HIRI by regulating the miR-34a/Nrf-2 pathway^[66,67]. H₂S significantly modulated miR-34a expression in hepatocytes, whereas crocin regulated its expression in serum. Both zinc sulfate and gallic acid decreased the miR-34a serum level of miR-34a as an anti-miR to ameliorate HIRI^[68-70]. Zheng *et al*^[71] revealed that high miR-34a-5p expression may reduce liver injury during hepatectomy in adults. Further, agomir-miR-34a-5p could attenuate HIRI in rats, and *in vitro* experiments indicated that miR-34a-5p/HNF4 α might be the underlying mechanism.

miR-122

miR-122 is a hepato-specific miRNA that accounts for nearly 70% of the total miRNAs pool in the liver tissue and exerts modulatory effects in liver diseases^[71-74]. Recent studies have implicated its role in HIRI. van Caster *et al*^[75] reported that miR-122 is a potential biomarker of warm HIRI of rats. In clinical research, serum miR-122 Levels were significantly elevated in patients with acute liver failure (ALF) than in healthy individuals. Further investigation revealed higher miR-122 levels in the serum and liver tissue of ALF survivors compared with those in the non-recovered patients^[75]. Furthermore, miR-122 downregulation is involved in the hepatoprotective effects of crocin, gallic acid, and zinc sulfate^[67-69]. However, John *et al*^[76] found that hepatocyte-specific miR122 deletion in mice exacerbated liver injury during HIRI and that nanoparticle-mediated miR122 overexpression attenuated liver injury. These controversial modulatory effects require further investigations.

miR-370

In 2009, miR-370 was detected in a mouse model of HIRI by using miRNA microarrays. Subsequent analysis revealed that miR-370 was upregulated and positively correlated with the severity of ischemic injury^[63,77]. Li *et al*^[78] reported that miR-370 was significantly upregulated in a mouse model of HIRI, and that miR-370 inhibition efficiently attenuated liver damage *via* TbrII. Further investigation revealed that downregulation of miR-370 reduced the levels of proinflammatory cytokines, but had no effect on the apoptosis and proliferation of hepatocytes during HIRI. Moreover, the NF-κB gene was suggested as a potential target of miR-370^[78]. Mesenchymal stem cells (MSCs) display immunomodulatory functions and have been proven to alleviate HIRI^[79-81]. Zare *et al*^[82] revealed that bone marrow-derived mesenchymal stem cells (BM-MSCs) downregulated miR-370 and inhibited inflammatory responses and apoptosis, thus attenuating liver damage during HIRI.

miR-494

In addition, miR-494 warrants further investigation. In a mouse model of HIRI, miRNA microarrays have indicated a upregulation of miR-494^[63]. Besides, miR-494 expression was reported to significantly increase during hypoxia for 4 h in L02 cells, and its overexpression protected against hypoxia-induced apoptosis^[82]. Another study suggested in a rat model of HIRI, miR-494 was elevated, and reducing its expression with propofol had a protective effect during HIRI^[83,84]. However, we observed an opposite trend in miR-494 expression of in other studies. Su *et al*^[85] showed that miR-494 was downregulated in a rat model of HIRI and H2O2-induced apoptosis in hepatic AML12 cells. Furthermore, overexpression of miR-494 attenuated HIRI by modulating the PTEN/ PI3K/ AKT signaling pathway^[85]. We speculated that the opposite trend of miR-494 during HIRI might be caused by the duration of ischemia and reperfusion, cell lines, and different models. Based on previous studies, the researchers chosen different durations of ischemia (75 min, 30 min, and 60 min), different durations of reperfusion (2 h, reperfusion moment, 6 h), and different cell models (hypoxia-induced apoptosis in L02 cells and H2O2-induced apoptosis in AML-12 cells) for their studies. Further studies are required to confirm this hypothesis.

In addition to these above miRNAs, many other miRNAs have been identified, including miR-17, miR-155, miR-223, miR-494, miR-27-5p, miR-191, miR-450-5p, and miR-218-5p. Functional tests revealed they might be involved in HIRI development by modulating various biological processes such as cell death, inflammatory immune responses, and oxidative stress by targeting different downstream genes. Tables 1 and 2 present detailed information on the upregulated miRNAs.

The downregulated miRNAs

Several miRNAs were downregulated and exhibited modulatory effects on HIRI. miR-146b, miR-124, miR-20b-5p, miR-133a-5p, miR-449b-5p, miR-9-3p, and miR-124-3p were significantly downregulated in a rat HIRI model^[85]. In terms of a mouse HIRI model, the downregulated miRNAs, including miR-330-3p, miR-1246, miR-142, miR-30b, miR-146a, miR-96, miR-125b-5p, miR-501-3p, miR-214, miR-142-3p, miR-24-3p, miR-141-3p, miR-194,

miR-124-3p, miR-140-5p, ¹miR-153-3p, miR-210-5p, miR-107-3p, miR-103-3p, miR-205-5p, miR-296-5p, miR-183-3p, and miR-698-5p were detected^[86,87]. Most of these miRNAs were confirmed and their functions were verified using cell models. Detailed information on the downregulated miRNAs is presented in Tables 1 and 2.

Only ⁸two miRNAs (miR-141-3p and miR-192-5p) have been identified in humans. Li *et al*^[88] collected serum samples from 27 Liver transplantation patients at different time points (pre-operatively, 4 h after reperfusion, and on postoperative days 1, 2, and 3) and measured the expression of miR-141-3p, ALT, and AST. They found that 4 h after perfusion, miR-141-3p was lower than pre-operation and then gradually increased over time, which manifested a negative correlation with ALT/AST levels^[87]. Roy and his colleagues detected miR-192-5p expression in the liver tissues and sera of patients with acute liver injury. The results shown that miR-192-5p decreased in liver samples, but elevated in serum levels from patients with acute hepatic injury; further investigation revealed that miR-192-5p concentrations in serum were positively correlated with AST, ALT, and miR-122 Levels, which might represent a hepatocyte-specific serum biomarker^[88].

Of note, several miRNAs have been indicated to participate in the hepatoprotective effect of several pharmacological agents during HIRI, including inhaled anesthetics and propofol. For instance, sevoflurane preconditioning ameliorates liver injury by the inhibitory effects of several miRNAs (*e.g.*, ¹⁹miR-133 and miR-205) on the Akt-GSK-cyclin D1 pathway^[89]. Others have reported that sevoflurane preconditioning promotes the expression of miR-96 and inhibits FOXO4, thus alleviating HIRI^[90]. In contrast, sevoflurane postconditioning exhibited the same hepatoprotective ¹⁴effect by counteracting miR-142 downregulation induced by I/R^[91]. Moreover, isoflurane upregulates miR-9-3p to protect rats from HIRI by inhibiting FNDC3VB^[92]. In addition, propofol exhibited protective effects against HIRI in rats by increasing the expression of miR-133a-5p and decreasing that of MAPK6^[93].

Collectively, HIRI alters the expression of miRNAs. In turn, differentially expressed miRNAs play vital roles in HIRI development. Currently, a lot of miRNAs have been

identified and their specific modulatory roles have been verified. However, it is important to note that human trials are lacking. Future research should focus on clinical transformation, which remains a significant challenge.

lncRNAs

²⁶ lncRNAs are a subset of noncoding RNAs with over 200 nucleotides (200 nt) and are localized to both the nucleus and cytoplasm^[8,119]. Typically, lncRNAs are ¹⁰transcribed by Pol II, and have 5'-end 7-methyl guanosine (m⁷G) caps and 3'-end polyadenylated [poly(A)] tails. lncRNAs were considered transcription junks without protein-coding capacity until their modulatory effects on gene expression were established. lncRNAs modulate chromatin structure and function, transcription, post-transcription, and sponge miRNAs by interacting with DNA, RNA and proteins, and in turn participate in diverse cellular processes such as cell differentiation, cell apoptosis, stem cell pluripotency, and stress response^[12,120,121]. Recent studies show that lncRNAs can affect various diseases (e.g., nervous disorders, immune systems, and cancers)^[122,123]. The role of lncRNAs in the pathophysiology of I/R has been explored in multiple oxygen-dependent organs, such as the heart, brain, and kidney^[124-129]. In terms of HIRI, it is still at an early stage. Here, we summarize the lncRNAs that have been reported, and detailed information is shown in Table 3.

In 2013, Chen *et al*^[130] first revealed that in mouse livers after I/R treatment, ²⁷ 71 upregulated lncRNAs (fold change ≥ 1.5 , and *P* value < 0.5) and 27 downregulated lncRNAs (fold change ≤ 0.7 , and *P* value < 0.5) were identified. Four up-regulated lncRNAs (AK139328, AK087277, AK054386 and AK028007) and six down-regulated ¹⁸ lncRNAs (AK143693, NR-028310, NR-015462, NR-036616, ENSMUST00000151138 and AK143294) were validated using quantitative reverse transcription polymerase chain reaction (RT-qPCR). Further investigation suggested that silencing of AK139328 could ameliorate HIRI by activating the Akt/ NF- κ B signaling pathway^[128]. The same research team detected the lncRNA profile in mouse plasma after HIRI and found that under the same criteria, 64 up-regulated lncRNAs and 244 down-regulated lncRNAs were detected.

The authors then conducted a comparative analysis of dysregulated lncRNA profiles between plasma and liver and revealed that all dysregulated lncRNAs in plasma remained either unchanged or absent in mice livers after HIRI, as did dysregulated lncRNAs in the livers, which strongly indicated that the source of these dysregulated lncRNAs may not be restricted to liver cells during HIRI^[129]. Another study suggested that blood cells secrete large amounts of lncRNAs during heart failure^[130,131].

With the development of novel technologies, an increasing number of differentially expressed lncRNAs have been identified, and their roles have been explored in HIRI models. Current studies indicate that lncRNAs participate in various biological processes involved in HIRI development. A few studies revealed that some lncRNAs, including TUG1^[132], NEAT1^[133], MALAT1^[134] and Hnf4αos^[135], could modulate the processes of apoptosis and inflammatory response. Other lncRNAs, such as MEG3^[136], Gm4419^[137], CCAT1^[138] and AK054386^[139] were verified to regulate apoptosis, whereas AK139328 was only found to regulate the inflammatory response^[130]. In addition to regulating these common biological processes, several lncRNAs participate in uncommon processes. HOTAIR expression in the liver was upregulated in a mouse model of HIRI, and further investigation indicated that HOTAIR regulates hepatocyte autophagy by targeting miR-20b-5p/ATG7^[140]. Similarly, HIRI downregulates the expression of KCNQ1OT1 in mice livers, which promotes proliferation and inhibits pyroptosis by serving as a competing endogenous RNA to modulate the miR-142a-3p/HMGB1 axis^[5]. Moreover, AK054386 upregulation may lead to sustained ERS and increased cell apoptosis and death in mice HIRI models^[139]. Detailed information is shown in Table 4.

Li *et al*^[141] successfully constructed HIRI-related lncRNA-miRNA-mRNA networks such as LOC1201029870-miRNA-331-3p/miRNA-128-5p-CDH3/UPK3B and LOC120094223-miRNA-92b-5p-KRT7, which may play an important role in HIRI. However, these specific modulatory mechanisms stay uncovered, and further investigation is needed.

In summary, these studies support the use of lncRNAs as highly attractive targets for diagnosing and treating HIRI. An increasing number of lncRNAs are known to be

involved in HIRI. Overexpression and knockdown of lncRNAs attenuated or aggravated the extent of HIRI *in vivo* and *in vitro*, respectively, indicating the significance of lncRNAs in HIRI. A comprehensive understanding of lncRNAs in HIRI not only provides a new dimension to the molecular mechanisms, but also paves the way for future treatments. Indeed, future studies need more functional experiments *in vivo* and *in vitro* to reveal the specific roles of lncRNAs and to further explore its secretory and transport mechanisms in HIRI.

CIRCULAR RNAS

Circular RNA is a special subclass of ncRNAs characterized by a covalent bond joining the 3' and 5' ends generated by the back-splicing of exons^[142-144]. Once produced, most circRNAs are exported from the nucleus to the cytoplasm^[145]. Compared to their cognate linear RNAs, circRNAs are more stable and are not easily degraded by RNase L, RNase P, or RNase MRP. In addition to regulating transcription, splicing, and chromatin interactions, circRNAs act as decoys for miRNAs and proteins, interact with proteins, and function as templates for translation, and as sources of pseudogene generation^[13,144]. circRNAs are involved in various biological processes, including immunity, neuronal function, cell proliferation, and transformation^[146-149]. Existing evidence indicates the potential of circRNAs in treating diverse diseases.

Advances in RNA sequencing technologies have allowed the detection and exploration of many circRNAs in various pathological conditions. Currently, circRNAs have been implicated in the process of I/R injury, particularly myocardial I/R injury. For instance, circ_SMG6 deteriorates myocardial I/R injury by activating the miR-138-5p/EGR1/TLR4/TRIF signaling, whereas circ_CNEACR and circ_ACR alleviate myocardial I/R injury by suppressing autophagy^[150-152]. Moreover, circ-FoxO3 attenuates blood-brain barrier damage by inhibiting mTORC1 activity during cerebral I/R^[153]. circ-AKT3 aggravates renal I/R injury by regulating the miR-144-5p /Wnt/ β -catenin pathway^[154]. However, only few studies have investigated the role of circRNAs in HIRI.

To date, only two studies have reported the potential role of circRNAs in HIRI. Zhang *et al*^[87] conducted a circRNA microarray in mice for the first time in 2019 and found that, compared to the sham group, 706 circRNAs were differentially expressed in the I/R group, including 213 upregulated and 493 downregulated circRNAs. Compared to the ischemic postconditioning (IPO) group, 641 up-regulated and 252 down-regulated circRNAs were identified in the I/R group (fold change ≥ 2.0 and P value < 0.05). Among these, circRNA_005186 was upregulated in the I/R group, whereas IPO treatment downregulated its expression. A subsequent *in vitro* experiment showed that circRNA_005186 functioned as a miRNA sponge for miR-124-3p, thereby enhancing EphA2 expression. In other words, the circRNA_005186-miR-124-3p-Epha2 pathway might be a possible protective mechanism of IPO against HIRI^[87]. The other five circRNAs (circRNA_011137, circRNA_013703, circRNA_29140, circRNA_36837, and circRNA_43819) were validated by RT-qPCR, and may be the focus of future research. In addition to IPO, IPC can attenuate HIRI. Tian *et al*^[155] reported the circRNA profiles of mice with ischemic livers, with and without IPC. The data revealed that there were 77 circRNAs and 686 mRNAs in the IRI group, 50 circRNAs and 95 mRNAs in the IPC group (fold change ≥ 1.5 , and P -value < 0.05), respectively, when compared with those in the sham group. Next, they compared the circRNA alterations in the three groups and selected circRNA_017753 for further study. The prediction of the circRNA-miRNA-mRNA pathway implied a potential role of the circRNA_017753-miR-218-5p/miR-7002-3p/miR-7008-3p-Jade1 pathway in the mechanisms of IPC protection in HIRI. However, further investigations are required^[155].

Although circRNA research in the field of HIRI is still in its infancy, the present data indicate great prospects for research. With the increasing attention of the scientific community, a thorough understanding of circRNA mechanisms will provide new insights and therapeutic targets for treating HIRI.

ADDITIONAL NCRNAS

Other ncRNAs ³ such as PIWI-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs) and tRNA-derived small RNAs (tsRNAs), have attracted widespread attention in recent years. For instance, some studies have revealed that piRNAs were abnormally expressed and might play a regulatory role in liver cancer, non-alcoholic fatty liver disease and liver injury^[156-158]. Moreover, snoRNAs and tsRNAs are involved in several liver diseases as biomarkers and therapeutic targets^[159-162]. However, only few studies have investigated their roles in HIRI. As our knowledge of these ncRNAs expands, their potential role in HIRI will be confirmed.

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