MicroRNAs in Hepatic Ischemia–Reperfusion Injury

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Hepatic ischemia–reperfusion injury (IRI) is one of the main factors for early allograft dysfunction (EAD), which may lead to graft rejection, graft loss, or shortened graft life in liver transplantation. Hepatic IRI appears to be inevitable during the majority of liver procurement and transportation of donor organs, resulting in a cascade of biological changes. The activation of signaling pathways during IRI results in the up- and downregulation of genes and microRNAs (miRNAs). miRNAs are ~21 nucleotides in length and well-characterized for their role in gene regulations; they have recently been used for therapeutic approaches in addition to their role as biomarkers for many diseases. Various miRNAs have been identified in association with hepatic IRI that either exaggerate or ameliorate the hepatic IRI. Altering targeted miRNA expression has great potential to reduce early graft dysfunction and improve patient outcome. Strategies to implement this approach have been studied using hepatic cell lines subjected to oxygen deprived conditions in vitro, as well as animal models after induction of hepatic IRI through warm ischemia in vivo. By studying the mechanisms of specific miRNAs, the up- or downregulation during hepatic IRI reveals whether that miRNA can ameliorate or exaggerate the metabolism and functions of the liver. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels can be used to indicate when liver injury is present and improve diagnosis accuracy along with miRNA biomarkers. The manipulation of miRNAs could have an influence on the inflammatory and oxidative stress pathways associated with hepatic IRI.

Keywords: microRNA ; ischemia–reperfusion injury (IRI) ; liver transplantation

1. Introduction

Liver transplantation is the only curative treatment for end-stage liver diseases. Despite the improvements in immunosuppression, graft loss after liver transplantation is still a major obstacle. One of the main problems is early allograft dysfunction (EAD) due to insult in the organ during transportation along with donor characteristics. One of the major risk factors for EAD is hepatic ischemia–reperfusion injury (IRI) [1]. IRI is a life-threatening condition which is caused by ischemia occurring during transportation of liver from donor site to recipient site and restoring the blood flow to the recipient following transplantation. Hepatic IRI progression has complex pathophysiology which activates multiple signaling pathways, including ischemia-induced cell damage and reperfusion-induced inflammation. If this progressive liver damage stays irreversible, it can lead to multi-organ dysfunction syndrome (MODS) or systemic inflammatory response syndrome (SIRS), leading to mortality in transplant patients [1][2].

IRI exacerbates cellular dysfunction due to the additional liver damage sustained during blood restoration to ischemic tissue [3]. Reactive oxygen species (ROS) mediate reperfusion through endothelial dysfunction and an inflammatory response, resulting in tissue damage [1][4][5]. Additional factors of IRI include oxidative stress, inflammatory cascades, cytokine storms, and Kupffer cells (KCs)/neutrophil activation [6][7].

Hypoxia of the tissues during transplantation results in decreased ATP from electron transport chain dysfunction. Due to the inhibition of ATP production, glucose metabolism results in an increase in lactic acid, which decreases the tissue pH [1][4]. Further metabolic dysregulation leads to a loss of ionic gradients from the inability of ATP-dependent ionic pumps to regulate Na^+, K^+, and Ca^{2+} [5]. ATP is degraded into hypoxanthine during ischemic conditions. When the tissue is reperfused, xanthine oxidase is catalyzed by the sudden increase in oxygen, resulting in the degradation of hypoxanthine to uric acid and superoxide anion [8]. Then, the highly reactive superoxide can be converted into hydrogen peroxide and the hydroxyl radical, which cause an inflammatory response through the dysregulation of cell permeability [8]. ROS continues to activate endothelial cells through NF-kB activation.

2. miRNA-122

miR-122 is liver-specific and highly expressed, accounting for almost 70% of the miRNA present in the liver, but increases significantly during hepatic IRI [9][10][11]. Therefore, the alteration of the miR-122 level could be utilized as a biomarker to predict liver recovery after transplantation [12]. IRI causes the upregulation of miR-122 in correlation with higher alanine

aminotransferase (ALT) and aspartate aminotransferase (AST) levels, which can serve as an indicator for liver injury [12]. miR-122 is regulated by the hypoxia-inducing factor-1α (HIF1α) transcription factor through the binding site within the miR-122 promoter [10].

In mice with HIF1α deletion, hepatocyte-specific miR122 initiation was prohibited [9]. With the complete deletion of miR-122 in mice, through isolating the dependence of HIF1α among miR-122 induction, studies have noted that prolyl hydroxylase domain (PHD1) is the target gene for miR-122 [9]. PHD1 is vital for maintaining protein stabilization through regulating HIF [9][10]. Through the ability to sense oxygen levels, PHD1 hydroxylates HIF1α except when there is lack of oxygen present; therefore, the tolerance for the body to handle hepatic ischemia is greatly reduced due to the repression of PHD1 levels when targeted by miR-122 [9]. Decreasing the levels of miR-122 by targeting HIF1α can be a promising therapeutic approach to promoting PHD1 expression and relief from hepatic IRI.

3. miRNA-450b-5p

miRNA-450b-5p suppresses Crystallin Alpha B (CRYAB), leading to increased inflammation stimulating hepatic IRI [13]. CRYAB has an anti-inflammatory impact on hepatic IRI by preventing IKKβ activation through reducing the canonical NF-κB pathway [13]. CRYAB can also relieve hepatic IRI through macrophage polarization targeting protein kinase B, which is inhibited by miRNA-450b-5p [13]. During hepatic IRI, miR-450-5p is upregulated in addition to IL-1β, tumor necrosis factor-α (TNF-α), and IL-6 [13]. Inhibiting miRNA-450b-5p could be used therapeutically to reduce severe inflammatory immune response and control hepatic IRI outcome in the clinic.

4. miRNA-155

miRNA-155 is upregulated by inflammatory mediators in association with innate and adaptive immune responses [14]. Mice with miR-155 deficiency had lower aminotransferase (ALT) levels [15]. One of the miR-155 targets is suppressors of cytokine signaling 1 (SOCS1). The downregulation of SOCS1 by miR-155 overexpression facilitates macrophage development and Th17 cell differentiation [15]. Liver macrophages trigger tissue inflammation and activate neutrophils specifically through macrophage phenotypes M1 and M2 [15]. M2 is the alternatively activated anti-inflammatory phenotype specifically used in tissue repair and homeostasis to enhance cell recovery that is upregulated when miR-155 is deficient [15][16]. miR-155 deletion also results in the suppression of IL-17 and inhibits the activation of Kupffer cells (KCs), resulting in a decrease in proinflammatory cytokines [17]. Overall, miR-155 deletion protects the mouse liver against IRI through the upregulation of SOCS1, resulting in less inflammation.

5. miRNA-191

Under ischemic/hypoxic conditions, miR-191 is upregulated, contributing to hepatic tissue damage and cell apoptosis [18]. miRNA-191 is also found to play a role in breast cancer through enhancing cell proliferation, migration, and chemoresistance [19]. When mice are subjected to hypoxia/reperfusion (H/R) stresses, miR-191 targets ZO-1-associated Y-box factor (ZONAB) [18]. miR-191 expression is mediated by hypoxia-inducible factor-1 at the promotor region [18]. ZONAB repression by miR-191 induces cell cycle arrest and apoptosis during hepatic IRI [18]. The miR-191 knockout mice showed less cell death and ischemic injury in comparison to the wild type [18]. The deletion of miR-191 appears to be a promising therapeutic approach to moderating liver tissue damage and cell death.

6. miRNA-370

During hepatic IRI, miRNA-370 is upregulated, causing inhibition of the transforming growth factor-β receptor II (TβRII) pathways and activation of the NF-κB pathway [20][21]. TβRII expression is a crucial receptor in the TGF-β signaling pathway through recruiting and phosphorylating the SMAD family of transcription factors [20]. Specifically through activation of SMAD 3, TNF-α and IL-1β expression are decreased while IL-10 is incre ased, inhibiting the activity of other inflammatory mediators to balance the immune response [22]. Hence, silencing miR-370 using antagomir-370 results in lower AST and ALT levels, indicating improvement for hepatic IRI [21].

7. miRNA-210

miR-210 was upregulated, leading to an increase in hepatocyte apoptosis during hepatic IRI [23]. miR-210 targets SMAD4 in the hypoxia pathway [23]. SMAD4 is suppressed when miR-210 is overexpressed. miR-210 knockout mice showed higher expression of SMAD4 and lower inflammatory markers and apoptosis [23]. Upon IRI, the miR-210 knockout mice had significantly lower ALT and AST levels in addition to lower TNF-α, IL-6, and IL-1β when compared to the wild-type

mice [23]. Inhibition of miR-210 is a potential strategy for decreasing cell apoptosis and inflammatory responses during hepatic IRI.

8. miRNA-34

miR-34 is increased during hepatic IRI, which regulates Sirtuin 1 (SIRT1) expression along with p53 [24]. SIRT1 is an NAD+-dependent deacetylase that plays an important role by downregulating the inflammatory response and suppressing reactive oxygen species (ROS) [25]. While evaluating the miR-34/SIRT1 pathway, mice were pretreated with carbon monoxide (CO) inhalation as a preconditioning treatment to promote anti-inflammatory effects [24]. Mice treated with CO and subjected to an hour of warm ischemia followed by 6 h of reperfusion had lower ALT serum levels and decreased neutrophil accumulation in comparison to the control group [24]. The CO was able to inhibit miR-34a, resulting in increased SIRT1 expression, which represses apoptosis and inflammatory pathways [24]. In mice with SIRT1 knockout, pro-inflammatory cytokines were increased through NF-κB acetylation, proving the importance of SIRT1 expression [24]. The ability of CO to downregulate miR-34 is a promising therapeutic strategy through targeting the miR-34 pathway in the liver [24].

9. miRNA-497-5p

miR-497-5p expression is upregulated during hepatic IRI in mice, and its role is further evaluated in isolated Kupffer cells (KC) [26]. When miR-497-5p is inhibited in mice, hepatocyte apoptosis, following hepatic IRI, is decreased [26]. MED1 is suppressed when miR-497-5p is upregulated, resulting in decreased TIMP2 expression. In miR-497-5p knockout, MED1 overexpression results in the inhibition of NF-κB through TIMP2 expression, as well as lower TNF-α/IL-1β expressions [26]. When miR-497-5p is downregulated, hepatic IRI is ameliorated in association with MED1/TIMP-2 activation, showing potential treatment for alleviating liver injury.

10. miRNA-128-3p

miR-128-3p suppresses Rho family GTPase 3 (Rnd3), thus activating the NF-κB pathway and transcription factor p65 upon hepatic IRI [27]. miR-128-3p knockout mice had higher levels of Rnd3 and lower levels of TNF-α, IL-6, and AST in the serum [27]. When upregulated during hepatic IRI, miR-128-3p activates NF-κB signaling and downregulates SIRT1 expression, inducing oxidative stress [27][28]. Therefore, inhibiting miR-128-3p can ameliorate liver injury through the Rnd3/NF-κB axis.

11. miRNA-146a

One of the most important miRNAs involved in the inflammatory response is miRNA-146a [2][29]. During the development of IRI, miRNA-146a is downregulated, causing an increase in inflammatory cytokines. Among the key associated factors in hepatic IRI pathogenesis, the interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF) are involved [30]. Specifically, miRNA-146a targets the Toll-like receptor 4 (TLR4) pathways by directly suppressing IRAK1 and TRAF6 [31]. The activation of TLR4 triggers a transmembrane signaling cascade, producing inflammatory cytokines including TNF-α and IL-6 [30]. It was shown that in mice, the overexpression of miR-146a protects the liver from hepatic injury [29][30]. miRNA-146a mimics could be used as a therapeutic agent to improve hepatic IRI by inhibiting the TLR signaling pathway, which leads to a decrease in the release of proinflammatory mediators.

Within the same miR-146 family, miR-146b is upregulated during hepatic IRI in contrast to the downregulation of miR-146a. miRNA profiles in porcine models of donation after brain death followed by circulatory death (DBCD) revealed an upregulation of miRNA-146b-5p [32]. Additional porcine models including donation after brain death (DBD) and donation after circulatory death (DCD) were evaluated in comparison to DBCD models and demonstrated that miR-7-1, miR-7-2, and miR-146b were significantly upregulated in the DBCD groups [32]. Further evaluated in 42 human samples, patients with high miR-146b expression also had EAD, revealing the potential use of miR-146b as a biomarker [32].

12. miR-194

miR-194 was down regulated in hepatic IRI, resulting in the upregulation of its target, pleckstrin homology-like domain family member 1 (PHLDA1) [33]. PHLDA1 activates TNF receptor-associated factor 6 (TRAF6), which exaggerates stress responses and inflammation during IRI through mitogen-activated protein (MAPK) initiation [33]. Impaired liver function was evident when PHLDA1 was overexpressed due to an increase in cytokines and chemokines [33]. miR-194 mimic and miR-

194 antagomir were used to compare results to evaluate the mechanisms of the miR-194/PHLDA1 axis [33]. When miR-194 was overexpressed, ALT and AST levels were lower, along with the lower expression of TNF-α, IL-6, IL-1β, and CXCL-10 [33]. Targeting PHLDA1 through the overexpression of miR-194 has potential as a therapeutic agent to ameliorate liver damage.

13. miRNA-140-5p

To identify the role of miR-140-5p in hepatic IRI, overexpression and knockout mice models were used to compare the results [34]. The study revealed that miR-140-5p is downregulated during hepatic IRI, resulting in an increase in inflammatory markers and cell apoptosis [34]. Whenever miR-140-5p is overexpressed in cells, inflammatory cytokines and cellular apoptosis are reduced due to the inhibition of CAPN1 [34]. miR-140-5p negatively regulates CAPN1, which is activated during hepatic IRI, leading to the overactivation of signaling cascades and cellular damage [34]. AML12 cells were also subjected to conditions of hepatic IRI with hypoxia regeneration models to provide further understanding of miR-140-5p during liver injury [34]. Since miR-140-5p overexpression can reverse apoptosis and decreases ALT and AST levels, miR-140 supplementation is a potential way to achieve better outcomes in patients after liver transplantation.

14. Additional miRNAs

In addition to the miRNAs listed above, there are some miRNAs which were studied mainly in vitro using cell lines and a hypoxia/reoxygenation model. For example, miR-142-3p is downregulated upon hepatic IRI. miR-142-3p downregulation results in the upregulation of its targets including myristoylated alanine-rich C-kinase substrate (MARCKS) in vitro in HepG2 cells [35]. MARCKS upregulates NF-κB expression, causing the p38/JNK signal to exaggerate inflammation [35]. MiR-142-3p mimic was transfected into AML-12 and HepG2 cell lines after subjection to hypoxia reoxygenation conditions to evaluate the mRNA levels of MARCKS [35]. When miR-142-3p expression was increased, inflammation and apoptosis were decreased through the suppression of the MARCKS signal, thus proving to be a valuable treatment for hepatic IRI [35].

Another miRNA which was recently identified to have a role in hypoxia/reoxygenation in vitro is miR-297. Transformed human liver epithelial-2 (THLE-2) cells were used to investigate miR-297 function in hepatic IRI [36]. miR-297 suppresses SIRT3 and modulates oxidative stress pathways, resulting in NOD-like receptor pyrin domain containing 3 (NLRP3) activation and NF-κB phosphorylation [36]. A miR-297 antagomir displays a great potential to improve hepatic IRI by promoting SIRT3 expression and inactivating NLRP3.

Lastly, miR-9-5p was studied in liver sinusoidal endothelial cells (LSECs) in vitro. Cells were subjected to oxygen and glucose deprivation to investigate the role of miR-9-5p in hepatic IRI [37]. miR-9-5p was downregulated and CXC chemokine receptor-4 (CXCR4) was upregulated, leading to an inflammatory response and decreased cell survival rate [37]. When miR-9-5p was overexpressed due to miR-9-5p mimic transfection to LSECs, CXCR4 was greatly reduced and decreased TNF-α, IL-6, and IL-1β levels [37]. miR-9-5p overexpression might be a therapeutic approach for protecting LSECs from IRI.

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