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REVIEW

MAPK Signaling Pathways in Hepatic Ischemia/Reperfusion Injury

Bo Yu*, Yalong Zhang*, Tianyu Wang, Jiayu Guo, Chenyang Kong, Zhongbao Chen, Xiaoxiong Ma, Tao Qiu

Department of Organ Transplantation, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Tao Qiu, Department of Organ Transplantation, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, People's Republic of China, Tel +86-13995632367, Email qiutao@whu.edu.cn

Abstract: The mitogen-activated protein kinase signaling pathway can be activated by a variety of growth factors, cytokines, and hormones, and mediates numerous intracellular signals related to cellular activities, including cell proliferation, motility, and differentiation. It has been widely studied in the occurrence and development of inflammation and tumor. Hepatic ischemia-reperfusion injury (HIRI) is a common pathophysiological phenomenon that occurs in surgical procedures such as lobectomy and liver transplantation, which is characterized by severe inflammatory reaction after ischemia and reperfusion. In this review, we mainly discuss the role of p38, ERK1/2, JNK in MAPK family and TAK1 and ASK1 in MAPKKK family in HIRI, and try to find an effective treatment for HIRI.

Keywords: ischemia/reperfusion injury, mitogen-activated protein kinases, liver

Introduction

Signal transduction by mitogen activated protein kinase (MAPK) is carried out in a three-level cascade. That is, the kinase of MAPKK kinase (MAPKKK) phosphorylates and activates MAPK kinase (MAPKK), then phosphorylates MAPK to activate it, and then translocates to the nucleus to regulate the basic physiological processes of cells.[1]

MAPKs are a group of highly conserved serine/threonine protein kinases that control cellular activity via signal transduction, substitution, amplification, and integration.[2] Dozens of members of the MAPKs family have been identified so far, and the role of apoptosis signal-regulating kinase 1(ASK1) and transforming growth factor β-activated kinase 1 (TAK1) of the MAP3K family in hepatic ischemia-reperfusion injury is increasingly studied in HIR.[3–7] MAPKKK acts on MAPKK to phosphorylate and activate it. Activated MAPKK then acts on MAPK family signaling molecules to phosphorylate and activate it. Activated MAPK enters the nucleus to regulate transcriptional regulation. We pay more attention to the function of extracellular signal regulated kinase 1 / 2 (ERK1 / 2), c-Jun N-terminal kinase (JNK) and p38MAPK in HIRI.

Hepatic ischemia/reperfusion injury (HIRI) includes "cold" IRI and "warm" IRI (which is very common in liver transplantation).[8–10] HIRI mainly involves hepatocytes, Kupffer cells (KCs) and immune cells including t cells and monocytes. The pathophysiological process is biphasic: initial ischemic liver injury and reperfusion injury after restoration of the blood supply.[11–14] During initial ischemic liver injury, blood flow into the liver is blocked, which results in local ischemia. The latter leads to hepatic hypoxia, consumption of adenosine triphosphate and glycogen, mitochondrial dysfunction and, eventually, hepatocyte necrosis.[15,16] Large numbers of inflammatory cells such as neutrophils, KCs, dendritic cells, circulating lymphocytes and monocytes infiltrate and accumulate in the damaged area. This action leads to the activation and secretion of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and other proinflammatory factors, which results in inflammatory reactions and direct damage to hepatocytes.[17,18] After restoration of the blood

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supply, activated KCs release many proinflammatory factors, which activate neutrophils and T cells further, and aggravate tissue damage.[19,20] Monocytes in the blood circulation are activated by proinflammatory factors and differentiate into macrophages with similar function to KCs, and are then recruited to the liver to maintain the immune response and amplify the inflammatory response further, which aggravates liver injury. IRI-mediated hepatocyte injury in a donor liver leads to poor liver function and acute/chronic rejection after transplantation, which limits clinical application of the donor liver.[19,21]

The mechanism of HIRI stated above involves cytokines and mediators, which are related to several cellular pathways (Figure 1).[13,22–24] If HIRI occurs, then p38, JNK and ERK are activated by specific cells to elicit a series of physiological and pathological reactions.[2,7,25] Therefore, these MAPK-related molecules are considered to be potential therapeutic targets for HIRI.

Role and Therapeutic Importance of p38 in HIRI

During HIRI, p38 is activated and participates in the inflammatory response of the liver.[26–28] In general, it is believed that p38 has a different role at different times and in different types of liver disease. In a non-steatotic liver, phosphorylation and activation of p38 are involved in the necrosis and apoptosis of hepatocytes.[29] In a steatotic liver, p38 is involved in liver inflammation because it induces reactive oxygen species (ROS) production indirectly.[9,30] Inhibiting the production or activation of p38 has a positive role in HIRI treatment.[31] Table 1 shows the current regulatory factors and therapeutic potential of p38 in HIRI.

Autophagy is a highly conserved program in eukaryotic cells. Autophagy plays an important part in counteracting adverse external stimuli such as IR.[32,33] An "inflammatory cascade" involving activated p38 and JNK is closely related to the aggravation of inflammation and autophagic cell death observed during HIRI.[34–36] Some scholars have reported that activation of p38 or JNK can be blunted by inhibiting expression of proinflammatory mediators such as TNF-α and IL-1β to reduce such inflammatory cascades. Apoptosis can be triggered by either external or internal factors, which is an important feature of HIRI pathogenesis. Inhibition of phosphorylation of p38 or JNK appears to protect against apoptosis, which can reduce HIRI or other types of acute liver injury.[37]

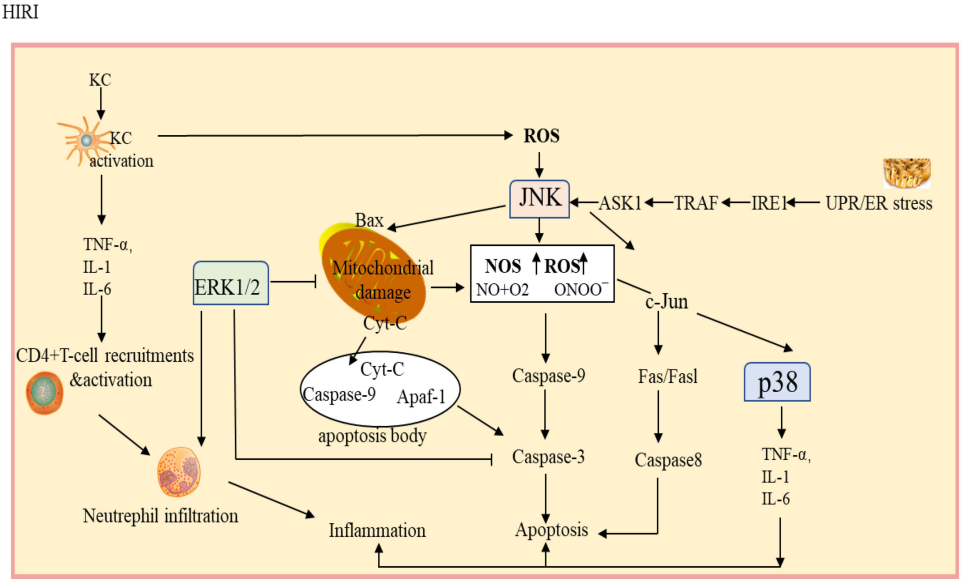

Figure 1 MAPK-related signaling pathways involved in hepatic ischemia-reperfusion injury. p38, Jnk and ERK participate in the regulation of liver ischemia-reperfusion injury through death receptor pathway, mitochondrial apoptosis pathway, endoplasmic reticulum reactive apoptosis pathway and oxidative stress pathway, etc.

Abbreviations: Cyt-C, cytochrome C; NOS, reactive oxygen species; NOS, nitric oxide synthase; ER, endoplasmic reticulum; TRAF, Tumor necrosis factor receptor-associated factor; IRE1, inositol requires enzyme 1; UPR, unfolded protein response; Apaf-1, apoptotic protease activating factor-1.3-kinase; RBP4, retinol binding protein 4; ROS, reactive oxygen species; SLPI, secretory leukocyte protease inhibitor; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule; X/XOD, xanthine/xanthine oxidase.

Table 1 Effect of Strategies That Regulate p38 in Experimental Models of Hepatic Ischemia-Reperfusion Using Livers

Target	Changes in p38 Induced by I-R	Treatment with p38 Modulators	Impact on HIRI	Target cell	Reference
P38	↑p38	BPS	↓	Hepatocyte	[37]
	↑p38	Acetazolamide	↓	Hepatocyte	[38]
	↑p38	FN-α4β1	↓	Hepatocyte	[39]
	↑p38	Salidroside	↓	Hepatocyte	[40]
	↑p38	ASX	↓	Hepatocyte	[42]
	↑p38	C19	↓	Hepatocyte	[43]
	↑p38	SB203580	↓	Hepatocyte	[48]

Acetazolamide has been used as a diuretic. However, Bejaoui et al showed that acetazolamide can improve HIRI by inhibiting activation of p38, ERK, and JNK.[38]

In vitro studies have shown that beraprost sodium (BPS) can inhibit TNF expression in human monocytes by inhibiting the phosphorylation of p38, JNK, and ERK-α to reduce lipopolysaccharide-induced inflammation. In the mesangial cells of rats, BPS has been shown to reduce ROS production and increase antioxidant activity, potentially preventing diabetic nephropathy. In vivo studies have revealed that BPS activity is related to its anti-inflammatory or antioxidant properties, and that the liver is an important target for BPS to intervene in acute or chronic progressive liver disease. As a result, BPS may be a promising HIRI treatment.[37]

CS-1 peptide-promoted blockade of interactions between fibronectin-a4b1 and integrins inhibits phosphorylation of p38MAPK (which is considered to be an attractive drug-intervention target), which suggests the regulatory role of fibronectin on activation of p38MAPK in HIRI. In addition, there is evidence that the p38MAPK kinase pathway controls fibronectin-mediated induction of matrix metallopeptidase (MMP)-9 and membrane-type matrix metalloproteins(MT1-MMP/MMP-14)by macrophages.[39]

One study on salidroside using mouse livers showed that it could protect hepatocytes from IRI by reducing the serum level of liver enzymes.[40] Those findings were confirmed by histopathology. Therefore, salidroside was postulated to inhibit activation of MAPK signaling (including phosphorylation of p38, JNK, and ERK) and protect hepatocytes from IRI. Salidroside ameliorated inflammatory infiltration, apoptosis and autophagy in damaged liver of mice.

Two studies focused on use of astaxanthin. After creation of a HIRI model, astaxanthin was administered: ROS production decreased. Also, expression of phosphorylated (p)-p38MAPK, p-ERK, and p-JNK in liver tissue decreased. That observation indicated that astaxanthin inhibited ROS production and phosphorylation activation of key proteins related to the MAPK family, which may be an important strategy to reduce apoptosis and autophagy.[41,42]

During HIR, the mRNA and protein expression of chemokine-like factor (CKLF)1 is upregulated. Immunohistochemical staining has shown neutrophil infiltration to be increased in ischemic livers, and myeloperoxidase activity to be increased significantly, after reperfusion. Levels of TNF-α and IL-1β are increased during HIRI. Administration of an antagonist of CKLF1, C19, was shown to significantly reduce levels of alanine aminotransferase-(ALT) and aspartate (AST) aminotransferase and the necrotic area of liver tissue. Further studies showed that C19 treatment suppressed phosphorylation of p38 and JNK.[43]

It has been reported that thioredoxin interacting protein (TXNIP) expression is upregulated in a rat model of HIRI.[44–47] In one study, TXNIP overexpression was found to upregulate phosphorylation of p38 and JNK significantly, and this effect was inhibited significantly by *TXNIP* knockout.[48] In addition, the p38-specific inhibitor SB203580 eliminated the effect of TXNIP overexpression on oxygen glucose deprivation/reoxygenation (OGD/R)-induced cell injury. Taken together, those results suggested that *TXNIP* knockout reduced hepatocyte IRI by preventing activation of the p38/JNK pathway. Therefore, TXNIP may be a new therapeutic target for HIRI treatment.

Role and Therapeutic Importance of JNK in HIRI

JNK, like p38, is activated during stress and inflammation, and participates in HIRI.[7,31,49–53] If IR occurs, JNK is activated by the ROS produced by mitochondria, which is an important factor in HIRI.[49,50] Previous studies have shown that inhibition of JNK activation attenuates HIRI.[31,51,54,55] However, some studies have shown that JNK activation can inhibit liver regeneration after liver transplantation, which may be related to the occurrence or severity of IRI after liver surgery. However, JNK plays an important role in HIRI. Studying the mechanism of action of JNK in HIRI treatment is very important.[31,56] Table 2 shows the current regulatory factors and therapeutic potential of JNK in HIRI.

Autophagy is a self-degrading and ubiquitous process in the body for recycling cellular contents, and protects organisms from various diseases (including HIRI). Activated JNK can induce B-cell lymphoma (Bcl)-2 phosphorylation, lead to separation of beclin-1 and Bcl-2, and lead to the death of autophagic cells. Therefore, the inflammation, apoptosis, and autophagy involved in HIRI are (at least in part) mediated by p38 and JNK signaling.[37]

Huang et al showed that simulation with microRNA (miR)-214 could reduce expression of TRAF1 (TNF receptor associated factor 1), p-ASK1 (Apoptosis signal-regulating kinase 1), and p-JNK in HIRI and inhibit the ASK1/JNK pathway. In their elegant study, miR-214 expression was downregulated in hepatocytes that underwent IRI and H/R, and miR-214 attenuates I/R-induced hepatocyte apoptosis by inhibiting the TRAF1/ASK1/JNK pathway, which expected to be a potential target for the prevention and treatment of HIRI.[57] N-acetylcysteine (NAC) inhibits I/R-mediated apoptosis and autophagy by affecting the JNK signaling pathway. The mechanism of action of NAC may involve weakening of expression of JNK and p-JNK by ROS-scavenging, an indirect increase in the Bcl-2 level and, finally, a change in the balance of expression between beclin 1 and Bcl-2. Phosphorylation of Bcl-2 can lead to separation of Bcl-2 from beclin 1, which reduces the inhibitory effect on beclin 1. Therefore, JNK activation can involve a change in the balance of expression between Bcl-2 and beclin 1, and may be the way that JNK regulates autophagy. Those results suggest potential clinical treatment of HIRI by NAC.[58]

Studies have demonstrated that JNK can affect mitochondria directly and cause apoptosis. JNK is activated during warm HIRI and cold HIRI induced by liver transplantation. Some studies have revealed expression of serine hydroxymethyltransferase (shmt)2 in a mouse model of IR. Wu and collaborators showed that impaired expression of shmt2 could induce JNK activation, promote apoptosis, and aggravate HIRI.[59]

Xu et al investigated the protective function and mechanism of action of propylene glycol alginate sodium sulfate (PSS) in a mouse model of HIRI. PSS pretreatment could significantly reduce histologic injury, release of transaminases, and production of proinflammatory cytokines. Compared with the control (IR model) group, PSS protected the liver from IRI by inhibiting MAPK signal transduction and downregulating inflammation, apoptosis.[60]

Role and Therapeutic Importance of ERK1/2 in HIRI

ERK1/2 is expressed widely in the human body. It is activated mainly by cell proliferation-related products, such as cell-growth factors, cell division-stimulating factors, and hormones.[61] It can also be activated by the extracellular matrix and ROS.[26,61,62] ERK1/2 is associated with proliferation, but some studies have shown that activation and expression of ERK1/2 can aggravate IRI,[63–66] which may be related to neutrophil infiltration and cell death.[67–70] While some studies also have shown that activation of ERK1/2 may protect against IRI,[71] which seems to be related to the time and severity of IR.[69,72–75] Table 3 shows the current regulatory factors and therapeutic potential of ERK1/2 in HIRI.

Table 2 Effect of Strategies That Regulate JNK in Experimental Models of Hepatic Ischemia-Reperfusion Using Livers

Target	Changes in JNK Induced by I-R	Treatment with JNK Modulators	Impact on HIRI	Cell model	Reference
JNK	↑JNK	miR-214	↓	Hepatocyte	[57]
	↑JNK	NAC	↓	Hepatocyte	[58]
	↑JNK	SHMT2	↓	Hepatocyte	[59]
	↑JNK	PSS	↓	Hepatocyte	[60]

Table 3 Effect of Strategies That Regulate ERK1/2 in Experimental Models of Hepatic Ischemia-Reperfusion Using Livers

Target	Changes in ERK1/2 Induced by I-R	Treatment with ERK1/2 Modulators	Impact on HIRI	Cell model	Reference
ERK1/2	↑ERK1/2	Caffeic alcohol	↓	Hepatocyte	[76]
	↑ERK1/2	LIPOC	↓	Hepatocyte	[77]
	↑ERK1/2	L-THP	↓	Hepatocyte	[78]
	↑ERK1/2	AnisidinellA	↓	Hepatocyte	[79]
	↑ERK1/2	CO	↓	Hepatocyte	[80]
	↑ERK1/2	T3	↓	Hepatocyte	[81]

Many scholars have reported the ERK pathway to be closely related to the inflammatory response, apoptosis, and autophagy. Inhibition of the ERK pathway has been found to be protective during HIRI. Studies have shown that peroxisome proliferator activated receptor (PPAR)γ expression is closely related to the proliferation, differentiation, and apoptosis of cells. In addition, several studies have shown that p-ERK can activate PPARγ. Caffeic alcohol inhibits inflammation, apoptosis, and autophagy through the ERK/PPARγ pathway, thereby protecting the liver (at least in part) from damage during IRI. Further experimental verification of that postulated mechanism is needed.[76]

Limb ischemic postconditioning (lipoc) is a method employed to reduce IRI. In a study on the protective effect of lipoc on HIRI and its mechanism of action, lipoc helped to protect against HIRI in rats, but this protective effect could be eliminated by a blocker of ERK1/2: PD98059. Hence, Liposomes mediate protection against IRI through activation of the ERK1/2 signaling pathway. However, how ERK1/2 may have a protective role after being activated by lipoc needs to be studied further.[77]

Studies have shown that L-tetrahydropalmatine (L-THP) pretreatment can reduce IR-induced hepatocyte injury and secretion of proinflammatory cytokines such as IL-6 and TNF-α. In addition, L-THP can inhibit the ERK/nuclear factor-kappa B (NF-κB) signaling pathway, thereby inhibiting the apoptosis and autophagy of hepatocytes. The protective effect of L-THP has been shown to be positively correlated with its dose.[78]

Wang et al used a HIRI model in mice to investigate the role of T lymphocytes in regulating autophagy and their subsequent protective effect on hepatocytes. Pretreatment with anisidineIIA before HIR could enhance the autophagy of hepatocytes significantly through the MEK/ERK/mammalian target of rapamycin (mTOR) pathway. Enhanced autophagy could reduce ROS production by scavenging damaged mitochondria so as to protect against HIR. This protective effect was manifested in a reduced serum level of enzymes, liver-tissue injury, infiltration of inflammatory cells, proinflammatory cytokines, and hepatocyte apoptosis.[79]

Carbon monoxide (CO) is a product of heme-oxygenase degradation. CO has been shown to provide cellular protection in various models of tissue injury. Some studies have investigated the effect of exogenous inhalation of CO on cold IR after liver transplantation. Cold HIRI was found to be related to the rapid phosphorylation of MAPK in liver grafts 1 h after orthotopic liver transplantation, and to significantly inhibit phosphorylation of ERK1/2, MAPK, an upstream transcription factor (MEK1/2) and downstream transcription factor (c-myc). Those results showed that exogenous CO could: (i) inhibit expression of early proinflammatory and stress-response genes, and improve HIRI; (ii) downregulate the MEK/ERK1/2 signaling pathway.[80]

Yang and collaborators studied triiodothyronine (T3) treatment in male C57BL/6 mice that underwent HIRI. Mice pretreated with T3 before IR induction showed increased autophagy mediated by the MEK/ERK/mTORC1 pathway. Pretreatment with T3 could protect against HIRI by enhancing autophagy. Therefore, T3 preconditioning may be a potential method for HIR treatment.[81]

Role and Therapeutic Importance of ASK1 in HIRI

The initiation of MAPK cascade can be initiated by the pressure of cell membrane receptors, intracellular inflammatory response bodies, or organelles such as mitochondria and endoplasmic reticulum. However, the sustained activation of

MAPK requires the involvement of ASK1. ASK1 is usually inactivated by binding with various inhibitors such as thioredoxin or glutathione transferase.[82] These inhibitors are redox sensitive. Therefore, ROS generated in the process of hepatic ischemia-reperfusion injury can activate ASK1 from the inhibited state and aggravate the inflammatory injury through the downstream JNK signaling pathway. Thus, JNK and ASK1 remove irreparably damaged cells through mechanisms that regulate endoplasmic reticulum stress and mitophagy.[83] Table 4 shows the current regulatory factors and therapeutic potential of ASK1 in HIRI.

Some studies have found that the expression of toll interacting protein (Tollip) is closely related to the process of HIRI. RNA sequencing analysis and phenotypic detection showed that Tollip deficiency could significantly reduce HIRI in vivo and in hepatocytes. Tollip is a regulator of HIRI by promoting ASK1 N-terminal dimerization and the resulting activation of JNK/p38 signal. Inhibiting Tollip or its interaction with ASK1 may be an effective strategy to treat HIRI.[84]

Adenosine receptors (ARs) are potentially effective therapeutic targets for liver diseases. The effects of drugs on A2AR and A1R activation were studied. CGS21680, an A2AR agonist, protected primary adipose mouse hepatocytes from IR-induced ASK1 and JNK activation. This effect was attributed to the inhibition of ASK1 by PI3K/Akt. In contrast, the A1R agonist CCPA increased IRI, intracellular lipoatrophy, and oxidative species (OS) production, which increased lipid/OS-dependent ASK1-JNK stimulation. These findings point to a new mechanism for CGS21680-mediated hepatoprotection: PI3K/Akt-dependent inhibition of ASK1. CGS2168 and CCPA may reduce or increase IRI in fatty liver by inhibiting or activating the cytotoxic ASK1/JNK axis, respectively.[85]

DUSP12 belongs to the DUSP (dual specific phosphatase) family and some DUSPs have been identified as being involved in HIRI regulation. Researchers found a significant decrease in DUSP12 expression in the mouse model of HIRI in vivo and the hypoxia / reoxygenation (H/R) model in vitro in one study. The study discovered that DUSP12 attenuated I/R-induced liver injury in DUSP12 transgenic mice. Furthermore, both in vitro and in vivo, DUSP12 inhibited hepatic inflammatory responses and attenuated apoptosis. ASK1 is required for DUSP12 to play its role in HIRI, and inhibiting ASK1 prevented inflammation and apoptosis in DUSP12 deficient mice and hepatocytes. The ASK1-JNK/p38 signaling pathway is primarily responsible for DUSP12's regulatory role.[86]

F-box/WD repeat-containing protein 5 (FBXW5) is a key regulator of stress signaling and has recently been reported to be involved in liver immunity. In one study, inhibition of FBXW5 was found to significantly reduce MAPK and nuclear factors κB kinase (IKK) inhibitor pathway, leading to cytokine release, liver pathological damage and apoptosis. Overexpression of FBXW5 achieved the opposite effect. Studies on its mechanism have shown that FBXW5 exacerbates liver inflammation by promoting the phosphorylation of ASK1, and blocking TRAF6 can eliminate this process. Indicating that FBXW5 may become a key accelerator of HIRI by enhancing the activation of ASK1 in a TRAF6 dependent manner.[87]

Caspase recruitment domain family member 6 (CARD6) was initially shown to be expressed in NF- κB plays an important role in activation. Some researchers found that the expression levels of CARD6 were significantly down-regulated in transplanted livers after exposure to IRI in liver transplant patients and mouse liver transplant models, and

Table 4 Effect of Strategies That Regulate ASK1 in Experimental Models of Hepatic Ischemia-Reperfusion Using Livers

Target	Changes in ASK1 Induced by I-R	Treatment with ASK1 Modulators	Impact on HIRI	Cell model	Reference
ASK1	↑ASK1	Tollip	↓	Hepatocyte	[84]
	↑ASK1	CGS21680	↓	Hepatocyte	[85]
	↑ASK1	CCPA	↑	Hepatocyte	[85]
	↑ASK1	DUSP12	↓	Hepatocyte	[86]
	↑ASK1	FBXW5	↑	Hepatocyte	[87]
	↑ASK1	CARD6	↓	Hepatocyte	[88]
	↑ASK1	GALNT4	↓	Hepatocyte	[89]
	↑ASK1	RNF5	↓	Hepatocyte	[90]

explored the molecular mechanism of CARD6 function in vivo and in vitro. CARD6 was found to be a new protective factor against HIRI, which inhibits inflammation and hepatocyte death by inhibiting ASK1 signaling pathway.[88]

Glycosyltransferases have been identified as potential targets for the treatment of HIRI, but their role in HIRI remains to be studied. We investigated the exact function and molecular mechanism of the glycosyltransferase N-acetylgalactosaminytransferase-4 (GALNT4) in HIRI. It was found that there was a close correlation between GALNT4 expression and HIRI related molecular events in mouse models. In patients receiving liver transplantation and mouse models, GALNT4 expression levels were significantly upregulated after reperfusion surgery. We found that GALNT4 overexpression significantly attenuated the extent of I/ R-induced liver parenchymal injury, inflammatory cell infiltration and hepatocyte death, whereas GALNT4 knockdown resulted in the opposite phenotype. In contrast, mechanistic studies suggest that GALNT4 directly binds ASK1 and inhibits its n-terminal dimerization and subsequent phosphorylation, leading to robust inactivation of downstream JNK/p38 and NF-κB signaling. Interestingly, the inhibitory ability of Galnt4 on ASK1 activation was independent of its glycosyltransferase activity.[89]

RNF5 plays an important role as an E3 ubiquitin ligase in the regulation of cell differentiation, growth and transformation. It has been found that RNF5 is significantly downregulated during HIR in mice and hepatocytes. Subsequently, RNF5 knockdown and cell line overexpression were stimulated by hypoxia reoxygenation. The results showed that inflammatory infiltration and hepatocyte apoptosis were significantly increased in the liver of RNF5 knockout mice, while RNF5 overexpression attenuated IR-induced liver injury. Mechanistically, RNF5 interacts with phosphoglycerate mutase family member 5 (PGAM5) and mediates the degradation of PGAM5 k48-linked ubiquitination, thereby inhibiting the activation of the ASK1/JNK/p38 pathway. This ultimately suppressed the inflammatory response and apoptosis in HIRI.[90]

Role and Therapeutic Importance of TAK1 in HIRI

TAK1 is a NF- κB and intracellular protein kinase upstream of JNK, which takes an important part in HIRI. The autophosphorylation of TAK1 is dependent on the ubiquitination regulation of TAK1 itself.[91] Ubiquitination and deubiquitination are essential for regulating TAK1 mediated activation and have been confirmed in numerous disease model studies.[92] Table 5 shows the current regulatory factors and therapeutic potential of TAK1 in HIRI.

Ubiquitin specific peptidase 4 (USP4) protein is a deubiquitinated enzyme related to many important biological processes. A study has explored the role of USP4 in HIRI. The results showed that USP4 was significantly upregulated in the liver of mice suffering from HIRI. USP4 knockout mice showed aggravated HIRI. In addition, Overexpression of USP4 reduced hepatic inflammatory infiltration and apoptosis upon HIR stimulation. USP4 deficiency has adverse effects on HIRI by inducing the activation of TAK1 / JNK signaling pathway. Studies have shown that USP4 deficiency plays a harmful role in HIRI by promoting the activation of TAK1 / JNK signaling pathway.[93]

Ternary motif (TRIM)8 is an E3 ubiquitin ligase that interacts with and ubiquitinates with a variety of substrates and is closely related to innate immunity. A study has explored the role of TRIM8 in HIRI. The results showed that TRIM8 was significantly upregulated in the liver of mice suffering from HIRI. TRIM8 knockdown can alleviate the injury of hepatocytes caused by I/R. In vitro and in vivo, inhibition of TRIM8 expression alleviates hepatic inflammatory response and inhibits apoptosis. Mechanistically, studies have shown that TRIM8 deficiency may alleviate IRI by inhibiting the

Table 5 Effect of Strategies That Regulate TAK1 in Experimental Models of Hepatic Ischemia- Reperfusion Using Livers

Target	Changes in TAK1 Induced by I-R	Treatment with ASK1 Modulators	Impact on HIRI	Cell model	Reference
TAK1	↑TAK1	USP4	↓	Hepatocyte	[93]
	↑TAK1	TRIM8	↑	Hepatocyte	[94]
	↑TAK1	DUSP14	↓	Hepatocyte	[95]
	↑TAK1	STEAP3	↑	Hepatocyte	[96]
	↑TAK1	CREG	↓	Hepatocyte	[97]

activation of TAK1 and its downstream JNK/P38 pathway. TAK1 requires TRIM8 function in HIRI, because TAK1 activation abrogates TRIM8 function in vitro. In addition, TRIM27 was found to be a key regulator of HIRI by mediating the degradation of TAK1 binding protein(TAB)2/3 and the inhibition of downstream TAK1-JNK/p38 signal. TRIM27 may be a promising method to protect the liver of transplant recipients from I / R-mediated hepatocyte injury.[94]

The investigators found that DUSP14 was significantly down regulated in liver tissues of liver transplant patients and mice undergoing liver I/R surgery. DUSP14 knockout and DUSP14 transgenic mouse models showed that DUSP14 reduced cell death, improved inflammation, and promoted hepatocyte proliferation/regeneration. Dusp14 also inhibits MAPK and NF-κB signaling through physical interaction with TAK1. The results show that DUSP14 is a protective factor of HIRI, and DUSP14 plays an important role in ameliorating HIRI by inhibiting the TAK1-JNK1/2 pathway. Targeting regulation of this axis may be a novel strategy to prevent or intervene in this pathological process.[95]

Six-transmembrane epithelial antigen of the prostate (STEAP3) are key regulators of iron uptake and participate in the immune and apoptotic processes of various cell types. In one study, researchers found that STEAP3 expression was significantly upregulated in the liver tissues of mice undergoing liver I/R surgery and primary hepatocytes subjected to hypoxia/reoxygenation injury. Subsequently, the molecular mechanism of STEAP3 function was explored in vivo and in vitro. The results showed that STEAP3 deficiency could inhibit TAK1 activation and downstream JNK and p38 signaling. STEAP3 is a mediator of HIRI and regulates inflammatory response and apoptosis through TAK1 dependent activation of JNK/p38 pathway.[96]

The cellular repressor of E1A-stimulated genes (CREG) is a key regulator of cell proliferation, plays a protective role in cardiovascular disease, and is involved in steatosis and inflammatory responses in the liver. However, other effects of CREG on the liver and on IRI are unknown. However, the role of CREG in HIRI remains largely unknown. One study used genetic engineering technology to explore the role of CREG in HIRI and found that CREG inhibits MAPK signaling by inhibiting TAK1 phosphorylation. The results showed that CREG could prevent HIRI. CREG plays a protective role in HIRI by directly interacting with TAK1 and inhibiting the phosphorylation of TAK1 and activation of the downstream JNK/p38 pathway, thereby attenuating the inflammatory response and apoptosis.[97]

MAPK Pathway in KCs

KCs participate directly in the inflammatory process during HIRI. Therefore, exploring the role of MAPK pathways in KCs is very important when studying HIRI. Recent studies on KCs in HIRI are as follows. (Tables 6).

Liu et al showed that KCs increased levels of urotensin II (UII), urotensin II receptor (UIIR), TNF-α, and IL-1β significantly after stimulation with lipopolysaccharide. Pretreatment with uranyl peptide (UIIR antagonist) could significantly inhibit the effects of lipopolysaccharide stimulation of KCs in terms of expression of UII/UIIR, TNF-α, and IL-1β. LPS stimulation induced phosphorylation of nuclear p38MAPK and NF-κB, expression of the p65 subunit, and enhancement of NF-κB binding activity to DNA molecules, whereas pretreatment with uranyl peptide significantly inhibited the nuclear expression and activity of these molecules stimulated by lipopolysaccharide in KCs. Therefore, the

Table 6 Effects of Strategies to Regulate MAPK on KCs

Target cell	Functions	Impact on HIRI	Treatment	Reference
Kuffers	Promote the activation of inflammatory pathways and the release of various inflammatory factors	Inhibit the production of inflammatory factors in kuffer cells	Uranyl Peptide	[98]
			Zinc	[99]
			USP25	[103]
			Allicin	[106]
			SAM	[122]
			ISO	[107]
			PKC-ζ	[111]
		Coordination of macrophage polarization types(M1-M2)	IL-22	[110]
			LECT2	[110]

UII/UIIR system may mediate the production and release of lipopolysaccharide-stimulated proinflammatory cytokines through KCs. This mediating effect may be dependent (at least in part) on p38MAPK and NF-κB.[98]

Adequate zinc levels are essential for reducing inflammatory processes in the body, and studies have shown that zinc supplementation can improve the prognosis of patients with chronic liver disease.[99–101] Some studies have discussed the clinical application of serum zinc in patients with chronic liver disease and the anti-infection mechanism of zinc supplementation.[99] Zinc pretreatment has been found to increase the level of lactate dehydrogenase in KCs and HSCs, and reduce gene expression of myeloid differentiation primary response (MyD)88, MAPK, and NF-κB. Those data indicate that zinc supplementation acts on KCs through a MyD88/MAPK-related pathway to reduce the inflammatory effect on the liver.

Inhibition of tumor necrosis factor receptor related factor (TRAF)3 degradation induces endotoxin tolerance in macrophages.[102] However, the mechanism leading to TRAF3 inhibition is largely unknown. Ubiquitin-specific peptidase 25 (USP25) is a deubiquitinase. USP25 interacts with TRAF3 and stabilizes endotoxin tolerance in KCs.[103] The mechanism suggests that USP25 induces endotoxin tolerance in KCs by removing the TRAF3 K48-linked ubiquitin chain thereby inhibiting its degradation and reducing the phosphorylation level of downstream JNK/P38, promoting the secretion of the inflammatory factor IL-10.

Acrylamide in heated processed foods has attracted extensive attention because of its hepatotoxicity.[104] Allicin is a plant-derived antioxidant which has a significant protective effect against acrylamide-induced hepatotoxicity, but its mechanism of action is not known.[105] Steib et al studied the mechanism of action of allicin in KCs.[106] Allicin was found to inhibit activation of MAPK and NF-κB pathways and downregulate phosphorylation of JNK, ERK, p38, p65, and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). Allicin pretreatment seemed to inhibit acrylamide-induced inflammation.

The volatile anesthetic isoflurane has an immunomodulatory effect, whereas the fungal component fermentase induces inflammation through TLR2 or dectin-1 signaling pathways.[107,108] Wang et al studied the molecular effect of isoflurane (0.7%) on inflammatory activation of mouse KCs induced by fermentase.[109] In mouse KCs, isoflurane treatment significantly reduced fermentase-induced upregulation of cyclooxygenase-2 expression, prostaglandin E2 release, and the production of proinflammatory cytokines and chemokines. Wang et al showed (for the first time) that isoflurane treatment partially improved the fermentase-induced inflammatory response of KCs in vivo and in vitro by reducing ROS production, and that p38MAPK was regulated by ROS.

Su et al found that exogenous IL-22 significantly inhibited the fibrogenic factors and macrophage phenotype-changing factors secreted by M1 KCs while increasing the number of M2 KCs during the progression of carbon tetrachloride-induced liver fibrosis in mice.[110] A high M2/M1 KC ratio inhibited collagen production and HSC activation in a coculture of HSCs and KCs from mice treated with IL-22. These findings suggested that IL-22 could boost the ratio of M2 KCs to M1 KCs, slowing the progression of liver fibrosis. IL-22 promoted the polarization of lipopolysaccharide-treated macrophages from the M1 to the M2 phenotype, according to in vitro mechanistic studies. Cytokines achieved these effects by activating the signal transducer and activator of transcription (STAT)3 pathway while inhibiting the ERK1/2 and protein kinase C pathways.

Peng and collaborators transfected protein kinase C (PKC)-ζ small interfering RNA into a mouse KC line (mkcl3-2). Then, they treated the cells with elastase alone or an ERK inhibitor (U0126). The PKC-ζ protein/activity of cell extracts was determined, as was TLR-4 expression, NF-κB nuclear translocation, phosphorylation of ERK1/2, activated caspase-3, and DNA fragmentation. KC activation led to upregulated PKC-ζ activity, increased apoptosis, and induction of NF-κB nuclear translocation through an ERK1/2-dependent pathway. Inhibition of PKC-ζ activity in KCs significantly decreased apoptosis as well as activation of NF-κB and ERK1/2.[111]

Leukocyte-derived chemokine (LECT)2 is a hepatocyte factor that "senses" fat in the liver and whose expression is upregulated before weight gain.[112–114] LECT2 has been shown to selectively enhance lipopolysaccharide-induced JNK phosphorylation, but not to enhance phosphorylation of ERK or p38 in a mouse line of KCs (kup5). Consistently, LECT2 enhanced lipopolysaccharide-induced phosphorylation of two upstream activators of JNK: MKK4 (Mitogen-activated protein kinase kinase 4) and Table 2. The increase in LECT2 expression transformed the residual macrophages in the

liver into the M1-like phenotype and contributed to the development of liver inflammation.[115] Those findings revealed that the hepatocyte factor LECT2 could be used as a target for treatment of inflammatory diseases of the liver.

Conclusions and Perspectives

For various end-stage liver diseases, liver transplantation is the last option to save life. IRI is the first complication of liver transplantation. IRI involves complex mechanisms and has a huge impact on grafts. Avoiding or reducing IRI occupies the thoughts of all surgeons. MAPKs have great potential for the prevention and treatment of IR. p38, JNK, ERK1/2, ASK1 and TAK1 have been shown to have important roles in the occurrence and development of IR. We summarized some researches (Tables 1–6).However, some of the mechanisms are not clear, and some proteins have dual roles. For example, in most studies, inhibiting JNK helps reduce HIRI, but other studies have found that JNK activation inhibits liver regeneration after liver transplantation.These factors may be related to the type of liver, cold ischemia time, and other factors. Our goal is to discover how these different factors affect the liver and MAPKs, and whether study designs can be improved. After solving these problems, MAPKs could be important targets for HIRI treatment.

Autophagy is a highly conserved cellular program in the body. Through the regulation of autophagy related genes, cells can selectively transfer some specific organelles or metabolites to lysosomes for dissolution and transformation. Under stress, autophagy is considered to be a mechanism to protect cells. In the case of HIRI, autophagy can inhibit the production of ROS by mediating the phagocytosis of damaged mitochondria, and the production of ROS is the key link of liver IRI. Therefore, it is very important to find autophagy related regulators. In previous studies, it was found that inhibiting multiple members of MAPK family can enhance autophagy, indicating that HIRI can be effectively reduced by regulating related members of MAPK family.

LIPOC is a method to improve IRI, which has been studied more in recent years. Previous studies have found that LIPOC has a good protective effect on IRI of heart and kidney. Recently, it was found that LIPOC can protect the liver by activating ERK1 / 2 signaling pathway in HIRI. Compared with traditional ischemic preconditioning, LIPOC has stronger operability and less side effects. It is a good method to reduce HIRI, however, the specific mechanism needs to be investigated further. In addition, some other pre-treatment methods may also improve HIRI.For example, Fisetin can mediate GSK3β/AMPK/NLRP3 inflammasome pathway can fight inflammatory reaction and protect HIRI.[116]

In addition, we also pay attention to the polarization of intrahepatic macrophages. Due to their plasticity and activation mode, intrahepatic macrophages are mainly divided into classically activated macrophages (M1 type) and selectively activated macrophages (M2 type), while M1 type macrophages are mainly involved in initiating and maintaining inflammatory responses and M2 type macrophages are mainly involved in inflammation regression. If we can interfere with the polarization direction of macrophages, with M2 macrophages as the main differentiation direction, it will well protect hepatocytes. It is reported that miR-450b-5p suppressed alpha B-crystallin (CRYAB), CRYAB activates M2 polarization through Akt1/ mTOR target, thus alleviating HIRI.[117]

There are other ways and factors involved in the occurrence and development of HIRI. For example, miR-24-3p can improve the inflammatory response and cell apoptosis in HIRI process by targeting STING.[118] Liver selective MMP inhibition can prevent the hydrolytic cleavage of liver VEGF protein, thus enhancing the recruitment and implantation of bone marrow after liver injury.[119] This can improve the injury and accelerate liver regeneration. miR-125b protects liver from HIRI via inhibiting TRAF6 and NF-κB signal pathway.[120] FAM49B, constrained by miR-22, alleviates HIRI by inhibiting the TRAF6/IKK signal pathway in a Rac1-dependent manner.[121]

Taken together, we primarily concentrate on the related roles of p38, JNK and ERK1 / 2 in MAPK family in IR. It is worth noting that different researchers use different methods and time to create animal models, which may require more in-depth horizontal and vertical studies to compare these differences caused by different operation methods. At the same time, we also pay attention to some promising research, and discussed it in the previous article, hoping to provide some ideas for researchers.

Disclosure

The authors report no conflict of interest in this study.

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