Inflammatory Mediators of Liver Ischemia-Reperfusion Injury

Kyle B. Walsh,[1] Alexander H. Toledo,[2] Fernando A. Rivera- Chavez,[3] Fernando Lopez-Neblina,[4] Luis H. Toledo-Pereyra[1,5]

Abstract

Liver ischemia and reperfusion — which cause liver damage that is significant in a variety of diseases, injuries, and procedures (including but not limited to trauma and transplant) — have been the focus of many investigations in recent years. Although the mechanisms of ischemia-reperfusion injury are numerous and complex, many advances in treatment have been made. The following review considers recent advances in the understanding of hepatic ischemia-reperfusion injury and focuses on inflammatory mediators of significance. To provide a unique analysis and evaluation, we emphasized the most recent pertinent investigations of the last decade. Specific topics addressed include reactive oxygen species, nitric oxide, toll-like receptors, ischemic preconditioning, T cells, heme oxygenase-1, heat shock proteins, erythropoietin, selectins, protein kinases, matrix metalloproteinases, and cytokines.

Key words: *Ischemia and Reperfusion, Inflammatory mediators, Liver, Transplant, Trauma*

Ischemia-reperfusion injury, which involves complex inflammatory pathways, is a significant cause of liver damage and an important factor in a variety of diseases, injuries, and procedures that include (but not limited to) transplant and trauma. Several articles have provided an accurate review of the most important factors involved in hepatic ischemia and reperfusion (1,2), such as reactive oxygen species, nitric oxide (3-5), ischemic preconditioning (6), T cells (7, 8), heme oxygenase-1 (9), erythropoietin (10), c-Jun N-terminal kinases (11), matrix metalloproteinases (12), and chemokines (13). In this report, a comprehensive analysis of those factors is provided, and the fundamental molecular inflammatory mediators present after liver ischemia and reperfusion are discussed. Investigations involving animal models and human trials are reviewed, a summary of significant studies in human subjects is presented (Table 1), and the pathways and mediators important in liver ischemia-reperfusion injury are described (Figure 1).

From the [1]Michigan State University College of Human Medicine, East Lansing, Michigan; the [2]Division of Abdominal Transplantation, University of North Carolina, Chapel Hill, North Carolina; [3]University of Texas Southwestern Medical Center; [4]University of Baja California Medical School, Mexicali, B. C. Mexico; and [5]Kalamazoo Center for Medical Studies, Michigan State University, Kalamazoo, Michigan

***Address reprint requests to:** Luis H. Toledo-Pereyra, MD, Kalamazoo Center for Medical Studies, Michigan State University, 1000 Oakland Drive, Kalamazoo, MI 49008*

***Phone**: +1 269-337-6010 **Fax:** +1 269-337-4609 **E-mail:** toledo@kcms.msu.edu*

Experimental and Clinical Transplantation (2009) 2: 78-93

Reactive Oxygen Species

As liver ischemia ends and reperfusion begins, reactive oxygen species are one of the first elements formed (14). Reactive oxygen species include hydroxyl, the superoxide anion (15), and hydrogen peroxide. All reactive oxygen species respond in varying degrees at the initiation of reperfusion. The peroxidation of lipids (16, 17), protein oxidation, and the formation of peroxinitrites frequently occur after liver ischemia and reperfusion.

Liver ischemia-reperfusion injury is ameliorated by treatment with various free radical scavengers, as shown in investigations of allopurinol, superoxide dismutase, catalase, and other antioxidant compounds. Adenoviral delivery of superoxide dismutase has been shown to produce beneficial effects in warm ischemia reperfusion (18), alcohol-induced liver injury (19), and reduced-size liver grafts (20). The cytosolic superoxide dismutase is reported to be the most effective isoform in transplanted livers (21). Other free-radical scavengers that produce beneficial effects have been studied, including edaravone (MCI-186) (22-26), 2-mercaptoethane sulfonate (27,28), nitronyl nitroxide-

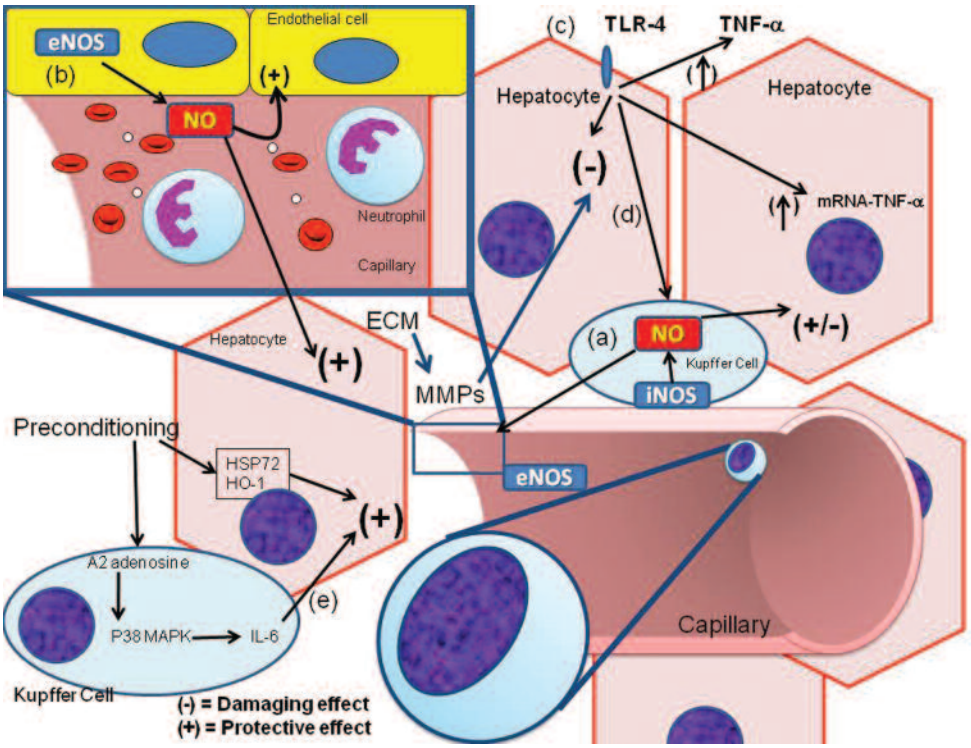

Figure 1. An illustration of the important mediators in the pathogenesis of liver ischemia reperfusion injury.

Table 1. Selected Liver Ischemia and Reperfusion Studies Involving Human Subjects

Reference	Procedure/Intervention	n	Conclusion
Kuyvenhoven et al. [216]	Orthotopic liver transplant	24	OLT is associated with a sharp increase in MMP-9, only MMP-9 appears to be involved in IRI during OLT
Kuyvenhoven et al. [217]	Orthotopic liver transplant	33	MMP-2 and MMP-9 do not relate to the late phase of hepatic IRI after human OLT
Taut et al. [188]	Orthotopic liver transplant	9	Protective effects of N-acetylcysteine treatment may be due to selectin shedding
Koneru et al. [93]	Deceased donor liver transplant	101	IP increased RI, an "IP paradox" in relation to evidence from studies of elective hepatic surgery
Amador, et al.[98]	Deceased donor liver transplant	60	IP for 10 minutes protects against IRI
Jassem, et al. [99]	Deceased donor liver transplant	23	IP is an effective method for protecting against IRI and is associated with a reduction in the nonspecific inflammatory response
Heizmann et al. [95]	Liver resection	61	IP protects against IRI
Choukèr et al. [104]	Partial liver resection	75	IP reduces the activation of neutrophils from the Pringle maneuver
Pulitanò et al. [130]	Liver resection (following intermittent portal clamping)	12	Local early expression of Th2 cytokines may help to attenuate injury
Guidi et al. [230]	Liver resection (during vascular occlusion of hepatic pedicle)	8	During surgical ischemic stress there is an increase of IL-6 more relevant in supra-hepatic vein blood
Choukèr et al. [102]	Partial hepatectomy	75	IP can reduce the unwanted degradation of adenine nucleotides to purines from Pringle maneuver
Boeri et al. [164]	Partial hepatectomy (for localized lesions)	10	HSP70 is induced by IRI, which appears to be beneficial
Chen et al. [34]	Elective hepatectomy (for liver tumor)	7	Melatonin reverses delayed apoptosis of neutrophils in receiving hepatectomy patients
	Laparoscopic cholecystectomy for gallstones	10	

Abbreviations: HSP, heat shock protein; IL, interleukin; IP, ischemic preconditioning; IRI, ischemia and reperfusion injury; MMP, matrix metalloproteinase; OLT, orthotopic liver transplant; RI, reperfusion injury; Th2, T-helper 2 cells.

amino acid conjugates (29), α-lipoic acid (30), ascorbic acid and mannitol (31), and metalloporphyrins (32). In this discussion of antioxidant molecules, it is also important to include melatonin, which exerts multiple protective effects in hepatic ischemia and reperfusion (33-36). Melatonin has been shown to reduce mitochondrial oxidative stress (37) and increase nitric oxide availability while reducing endothelin expression (38). A decrease in the level of tumor necrosis factor α and the expression of inducible nitric oxide synthase as well as a (possibly) preserved mitochondrial redox status have also been noted as a result of exogenous melatonin treatment (39). Recent evidence has shown that in cases of generalized ischemia after hemorrhagic shock, the effectiveness of melatonin in improving liver function depends on the melatonin receptor (40). In other studies, the beneficial role of melatonin in combination with other antioxidants such as carnosine (41), N-acetylcysteine (42), prostaglandin E1 analogue (43), and, in patients who have undergone partial hepatectomy, resveratrol (44) has been investigated.

Nitric Oxide

Nitric oxide is a free-radical diatomic gas that is produced from arginine (45) by nitric oxide synthase enzymes. Constitutive endothelial nitric oxide synthase and inducible nitric oxide synthase are expressed in liver cells. The process of ischemia and reperfusion is known to cause inducible nitric oxide synthase induction and activation, and there is evidence that interleukin (IL)-1β (46), IL-1 receptor (47), and IL-1 receptor along with nuclear factor-kappa beta (48) may have an important role in that induction. During ischemia and reperfusion, both helpful and harmful effects of nitric oxide have been reported, and the nitric oxide molecule has been described as having a "janus face" (3). These conflicting results about the role of nitric oxide during ischemia reperfusion, with some studies showing beneficial results and others harmful results, have been attributed to the use of nonspecific inhibitors of nitric oxide synthase (49), and it has been noted that whether nitric oxide has a helpful or harmful effect depends on several factors in the liver (4).

General nitric oxide synthase inhibitors have been found to exert a protective effect during liver IR in rats (50), and both endothelial nitric oxide synthase and inducible nitric oxide synthase deficiency have been shown to increase liver injury (51). There is also evidence that during hepatic ischemia and reperfusion, endothelial nitric oxide synthase is protective and inducible nitric oxide synthase is damaging (5). Endothelial nitric oxide synthase has been cited as the source of cytoprotective nitric oxide (52), and endothelial nitric oxide synthase deficiency has been shown to exacerbate injury (53). In other studies, inducible nitric oxide synthase is described as harmful (54-61) on the basis of investigations involving inducible nitric oxide synthase inhibitors (56-60) and inducible nitric oxide synthase knockout mice (61). In a study by Kurabayashi and colleagues, a nitric oxide donor exerted a protective effect by attenuating inducible nitric oxide synthase expression (62), and in another study, inducible nitric oxide synthase inhibitor ameliorated the negative effects of ischemia and reperfusion followed by lipopolysaccharide-induced endotoxemia (63). Nitric oxide production has also been associated with an imbalance in protein tyrosine phosphatases and apoptosis (64), and both nitric oxide and endothelin-1 have been implicated in the dysregulation of sinusoidal perfusion (65). The blockade of arginase has been shown to be beneficial in a murine model of partial warm ischemia reperfusion (66).

In contrast to the evidence of the harmful role of inducible nitric oxide synthase, as cited above, other studies have found a beneficial or inconclusive role for this enzyme. For example, there is evidence that adenovirus inducible nitric oxide synthase pretreatment is protective (67) and that Kupffer cells also protect the liver via an inducible nitric oxide synthase-dependent mechanism (68). In liver injury and fibrosis, the lack of inducible nitric oxide synthase has been associated with increased apoptosis and decreased necrosis and fibrosis (69). Hines and colleagues showed that inducible nitric oxide synthase deficiency produced unanticipated genetic alterations that made mice more susceptible to ischemia and reperfusion (70). A different study showed that the inhibition of inducible nitric oxide synthase produced nonstatistically significant benefits (71).

Lu and associates demonstrated that xanthine oxidase-derived nitric oxide protected the liver against ischemia-reperfusion injury (72). Von Knethen and Brüne (73) studied the activation of

peroxisome proliferator-activated receptor gamma by nitric oxide in monocytes and macrophages, and Crosby and colleagues (74, 75) examined the role of peroxisome proliferation-activated receptors in inhibiting inducible nitric oxide synthase. However, the role of nitric oxide during liver ischemia and reperfusion has not been established, and further investigations are needed to characterize that complex and important mediator.

Toll-Like Receptors

Toll-like receptors, which have recently been identified as modulators of liver ischemia and reperfusion (1, 76, 77), are homologues of *Drosophila* toll proteins that consist of 5 subfamilies (76) with 11 known members in humans. The activation of toll-like receptors results in the production of proinflammatory cytokines and costimulatory molecules (1). Fundamental roles proposed for toll-like receptors include generation of clonal adaptive immune responses, maintenance of normal homeostasis, and noninfectious disease pathogenesis (77).

Activation of toll-like receptor 2 and toll-like receptor 4 has been shown to be involved in the pathogenesis of hepatic ischemia-reperfusion injury. In one study, N-acetylcysteine inhibited that activation and was therefore defined as an agent that mitigates injury (78). According to Zhang and colleagues, inhibition of Kupffer cells is also beneficial because of the down-regulation of toll-like receptor 2 expression (79). Other investigations have found toll-like receptor 4 (but not toll-like receptor 2) to be necessary for the initiation of injury in models of hemorrhagic shock and resuscitation (80) and warm ischemia and reperfusion (81). Shen and colleagues showed that in murine models of orthotopic liver transplant, disruption of toll-like receptor 4 signaling had many beneficial effects (82), and the authors of another investigation suggested that inhibiting the toll-like receptor 4/nuclear factor-kappa beta pathway minimizes ischemia-reperfusion injury (83). In a plasmid expressed model, the IL-1–like protein ST-2 exerted a beneficial effect on warm hepatic IR injury, possibly by suppressing the toll-like receptor 4 pathway (84). Toll-like receptor 4 activation has been found to contribute to ischemia-reperfusion injury because of the release of tumor necrosis factor α (85), including lipopolysaccharide activation of toll-like receptor 4 (86), and in another study, toll-like receptor 4-deficient mice had less hepatic injury with the regulation of tumor necrosis factor α messenger ribonucleic acid reported as a critical effect (87). Carbon tetrachloride-induced injury has been shown to up-regulate the gene expression of toll-like receptor 4 (88). Tsung and colleagues demonstrated that the activation of actively phagocytic cells, like Kupffer cells, by toll-like receptor 4 is required for warm ischemia-reperfusion injury and inflammation (89). Those authors also showed that the nuclear protein high-mobility group box 1, a key alarm molecule during liver ischemia and reperfusion, is associated with toll-like receptor 4 signaling (90, 91).

Overall, the role of toll-like receptors during liver ischemia and reperfusion has not been completely defined. More studies are required to provide further information about those receptors and their interactions with other important molecules.

Ischemic Preconditioning

Ischemic preconditioning, which is a proposed method for reducing organ ischemia-reperfusion injury, involves exposing the organ to a brief period of ischemia (6), which will induce protective effects that will be beneficial during the more prolonged subsequent period of ischemia. Data concerning ischemic preconditioning are still inconclusive (92) and conflicting (93), and the precise mechanisms of that therapy are unknown (94).

Using ischemic preconditioning during ischemia and reperfusion has been shown to be beneficial in human subjects, resulting in less ischemic injury and fewer complications after hepatic resection (95) and in murine models of cirrhosis (96) and rat models of fatty liver disease (97). In a randomized controlled trial, 10 minutes of ischemic preconditioning was protective against ischemia-reperfusion injury in patients undergoing deceased donor transplant (98), and the results of another investigation suggested that ischemic preconditioning protects deceased donor allografts and reduces the nonspecific inflammatory response (99). However, Koneru and colleagues showed that ischemic preconditioning increased hepatic injury in recipients of a deceased donor liver transplant, although those authors acknowledged that their results conflicted with the findings of studies on elective hepatic surgery (93).

Various mechanisms that explain the beneficial effects of ischemic preconditioning have been identified (Table 2). The attenuation of nuclear factor-kappa beta and subsequent reduction of tumor necrosis factor α expression (94) or a reduction in oxidative stress, which protects mitochondria (100), are 2 such reported mechanisms. Other potential mechanisms include the stimulation of Kupffer cell-produced reactive oxygen species and liver regeneration via the A2 (adenosine) receptor pathway in Kupffer cells (101). The increased formation of A2 and the attenuated degradation of adenine nucleotides to purines (102) have been documented as well. Activation of the p38 protein and concomitant preservation of intracellular glutathione levels are essential for the development of hydrogen-peroxide resistance in preconditioned livers, although it has been shown that the A2 receptor is not essential for that process (103). Ischemic preconditioning was also found to reduce neutrophil activation in humans (104). IL-6 is reported to be a key mediator of protective effects in ischemic preconditioning (105). More specifically, that protection depends on IL-6 and its associated increased phosphorylation of signal transducer and activator of transcription 3 (106). Furthermore, cardiotrophin-1, a cytokine of the IL-6 family, has been shown to be a key mediator of the protective effects of ischemic preconditioning (107). Other data have suggested that suppression of tumor necrosis factor α may be involved in the protective mechanism of ischemic preconditioning against hepatic ischemia reperfusion injury (108).

In a study by Massip-Salcedo and colleagues, levels of heat shock protein 72 and the enzyme heme oxygenase-1 were elevated at 6 and 24 hours of reperfusion, respectively, as a result of ischemic preconditioning (109). Tyrosine kinases have been implicated as being involved in the ischemic preconditioning response (110), and protein kinase C is reported to be essential in studies of cold preserved hepatic grafts (111). Furthermore, the role of tyrosine kinases in ischemic preconditioning may be mediated by nuclear factor-kappa beta, but the effects of protein kinase C were found not to be dependent on nuclear factor-kappa beta (112).

Alternatives to traditional ischemic preconditioning, such as stepwise rising carbon dioxide insufflation (113) and preconditioning with death ligands (114), emulsified isoflurane (115), or high-mobility group box 1 (116), and their possible beneficial effects have been investigated. The possible benefits of ischemic preconditioning are still a topic of debate, however. An investigation of liver

Table 2. Protective Effects of Ischemic Preconditioning: Reported Mechanisms

Reference	Species	Factors	Reported Mechanisms of IP Protective Effects
Jassem et al. [99]	Human	Neutrophils	IP allografts showed no change in neutrophil or platelet infiltration after transplant
Choukèr et al. [104]	Human	Neutrophils	Reduces activation of neutrophils elicited by the Pringle maneuver
Choukèr et al. [102]	Human	Adenosine	Increases formation of adenosine, and can reduce the unwanted degradation of adenine nucleotides to purines from the Pringle maneuver
Ricciardi et al. [110]	Pig	Tyrosine Kinases	Protects the liver from sustained cold ischemia and tyrosine kinases are involved
Ricciardi et al. [111]	Pig	PKC	Modulation of PKC is essential for responses in the cold preserved hepatic graft
Lee et al. [100]	Rat	Mitochondria	Protects the mitochondria from harmful effects of IR, and is associated with the reduced oxidative stress
Arai et al. [101]	Rat	Kupffer Cells	Protects hepatocytes through stimulating Kupffer cells to produce ROS, and promotes regeneration via A2 receptor pathway in Kupffer cells
Schauer et al. [103]	Rat	p38 MAPK Glutathione A2a receptor	The activation of p38 MAPK and preservation of the intracellular glutathione system, but not A2a receptor stimulation, seems to be pivotal for protective effects
Shinoda et al. [108]	Rat	TNF-alpha	Protective effects may involve TNF-alpha suppression and subsequent microcirculatory regulation
Massip-Salcedo et al. [109]	Rat	HSP72 HO-1	Increases HSP72 and HO-1 at 6 and 24 hours of reperfusion, respectively
Iñiguez et al. [106]	Rat, Mouse	Cardiotrophin-1	Cardiotrophin-1 is a key mediator of the protective effects, and is an essential endogenous defense against IR
Funaki et al. [94]	Mouse	NF-kappaB TNF-alpha	IP attenuates NF-kappaB activation with subsequent reduction in TNF-alpha mRNA
Matsumoto et al. [104]	Mouse	IL-6	Protective effects are dependent on IL-6 signaling and are associated with increased phosphorylation of hepatic STAT3

Abbreviations: A2, adenosine 2; IP, ischemic preconditioning; MAPK, mitogen activated protein kinase; PKC, protein kinase C; ROS, reactive oxygen species.

transplants in pigs revealed no statistically significant beneficial effects of ischemic preconditioning, and the authors therefore called for further studies of the ischemic preconditioning process. (117). A study of deceased donor liver transplants showed that although ischemic preconditioning resulted in better tolerance to ischemia than did a standard orthotopic liver transplant, there was also decreased early function in the transplants treated with ischemic preconditioning. Those authors concluded that the clinical value of ischemic preconditioning remains uncertain (118). A recent Cochrane database review demonstrated that there is currently no evidence to support or refute the use of ischemic preconditioning in donor liver retrievals, and the authors suggested that further studies, including further clinical trials, are needed (6). DeOliviera and colleagues recently stated that in contrast to experimental studies using ischemic preconditioning, clinical studies include parameters that are much more heterogeneous and that there is still much to investigate in this area (92).

T Cells

Recent review articles have drawn attention to the importance of T cells in ischemia and reperfusion injury (7, 8). According to an emerging view, those cells can regulate liver ischemia-reperfusion–induced inflammation and can serve as novel targets for interventions (7). Because there is evidence that T cells have divergent roles in different phases of ischemia-reperfusion injury, their overall role in the ischemia reperfusion process is likely complicated (8). For example, although CD4+ T cells recruit neutrophils via IL-17, they also appear to attenuate neutrophil activation (119). Considering the ways in which T cells can function during ischemia-reperfusion injury, given the absence of exogenous antigens, it has been determined that CXCR3 chemokine biology has a critical role in the pathophysiology of hepatic ischemia reperfusion injury (120).

The immunosuppressant fingolimod has been shown to ameliorate hepatic ischemia and reperfusion injury by preventing T-cell infiltration (121). Other studies of T-cell costimulation via CD154-CD40 have identified that process as a potential therapeutic target (122, 123). Natural killer T cells have been implicated in ischemia-reperfusion damage, possibly due to their cytotoxicity (124). CD4 T cells have been shown to aggravate microvascular and hepatocellular injury by activating the endothelium and by increasing platelet adherence and neutrophil migration (125). In one study, the antagonism of IL-12 produced a beneficial effect by restoring apoptosis within peripheral T cells (126).

ATL-146e, an adenosine A2A receptor agonist, has been shown to produce beneficial effects such as the inhibition of the CD1d-dependent activation of natural killer T cells (127) and the concanavalin A activation of T cells (128). After ischemia and reperfusion, cyclo-oxygenase-2–deficient mice exhibited a significant reduction in liver damage, and the deficiency in cyclo-oxygenase-2 was found to favor a Th2 response (129). Furthermore, it has been suggested that the early expression of Th2 cytokines may contribute to the attenuation of liver ischemia-reperfusion injury in humans (130). The connecting segment-1 peptide blocks fibronectin-alpha4beta1 integrin interactions. Two studies have shown that treatment with connecting segment-1 significantly inhibited the recruitment of T cells and other factors that contribute to ischemia-reperfusion injury in rat models of orthotopic liver (131) and fatty liver transplants (132).

Heme oxygenase-1

Heme oxygenase-1 (heat shock protein 32) is an inducible rate-limiting enzyme that catalyzes the reaction of heme to carbon monoxide, iron, and biliverdin. Heme oxygenase-1 expression has been reported to be protective against various forms of stress and has therefore been considered for the treatment of several pathologic conditions (9).

Heme oxygenase-1 induction has been shown to be protective in cases of hepatic ischemia-reperfusion injury and in the reduction of oxidative stress, apoptosis, and inflammation in cirrhotic livers (133). Studies have used heme oxygenase-1 inducers and antagonists. The cobalt protoporphyrin induction of heme oxygenase-1 has been shown to improve liver function (including suppression of type 1 interferon) and histologic characteristics (134). Another investigation using cobalt protoporphyrin and the heme oxygenase-1 antagonist zinc protoporphyrin demonstrated the protective effects of heme oxygenase-1 induction during the prolonged storage of liver transplants (135). In one study, hypertonic

saline prevented ischemia-reperfusion injury by promoting the expression of heme oxygenase-1 (136), and in another investigation, induction with simvastatin preconditioning also had a protective result (137). In a study by Coito and colleagues, adenoviral heme oxygenase-1 gene transfer inhibited inducible nitric oxide synthase, prolonged the survival of steatotic orthotopic liver transplant in rats (138), and prevented CD95/FasL-mediated apoptosis (139). Heme oxygenase-1 overexpression has also been associated with decreased CXC chemokine ligand 10 expression (140). Heme oxygenase-1 has been studied in carbon-tetrachloride–induced liver damage, and induction had a possible protective effect (141, 142) in a study with glycyrrhizin, the major active component extracted from licorice (143). However, other data on carbon tetrachloride injury showed that a harmful effect resulted from higher heme oxygenase-1 activity (144). In a study of cold ischemia and reperfusion by Wang and colleagues, heme oxygenase-1 overexpression was protective, an effect that was attributed, at least in part, to modulation of the antiapoptotic pathway (145).

Finally, there is evidence that treatment with the products or related molecules of the heme oxygenase-1 reaction is protective, including biliverdin [146], bilirubin (147), and carbon monoxide. Specifically, exogenous carbon monoxide was protective in liver transplants (148, 149) and in carbon-tetrachloride–induced hepatic injury (150). There is also evidence that heme oxygenase-1 mediated cytoprotection depends on and can be substituted by carbon monoxide generation (151).

Heat Shock Proteins

Heat shock proteins, a class of molecular chaperones (particularly heat shock proteins 70 and 72), are reportedly involved in hepatic ischemia-reperfusion injury. In steatotic livers subjected to heat shock protein preconditioning, preventing the postischemic failure of microcirculation was associated with the induction of heat shock protein 72 and heme oxygenase-1 (152). Heat shock protein preconditioning also reduced the oxidative injury of cellular proteins and deoxyribonucleic acid (153).

The protective effects of other substances are also associated with heat shock protein induction. Prostaglandin E1 has been shown to induce heat shock proteins immediately after ischemia and reperfusion (154), and the mechanism of curcumin protection might be associated with the overexpression of heat shock protein 70 and antioxidant enzymes (155). In a study by Bedirli and colleagues, the natural antioxidant ergothioneine protected the liver by inducing the overexpression of heat shock protein, which caused the subsequent suppression of lipid peroxidation (156). The protective effects of 17beta-estradiol may be related to the overexpression of heat shock protein 70 (157). With regard to the apoptosis of hepatocytes caused by hydrogen peroxide and ethanol, geranyl-geranylacetone has been shown to exert an antiapoptotic action, at least in part via the priming of hepatocytes for enhanced heat shock protein 70 induction (158). Shi and colleagues demonstrated that quercetin pretreatment delayed liver regeneration via the inhibition of heat shock proteins (159), and although glutamine has been shown to be protective in ischemia-reperfusion in other tissues, its lack of effectiveness in the liver was attributed by Noh and colleagues to an absence of heat shock protein 70 up-regulation (160). In warm ischemia and reperfusion, the expression of heat shock protein 70 and the Bcl-2 family were found to be effective markers of viability (161), and in cold preservation, the beneficial effects of doxorubicin (162) and zinc (163) were associated with heat shock protein induction. Heat shock protein 70 induction during ischemia and reperfusion injury has been associated with a prompt reduction in the levels of transaminases and the rapid recovery of fibrinogen (164).

In considering the possible downstream effects of heat shock proteins during ischemia and reperfusion, heat shock protein preconditioning protected the liver by suppressing nuclear factor-kappa beta and stabilizing I-kappa beta in a study by Uchinami and colleagues (165), and heat shock protein inhibition of the activation of nuclear factor-kappa beta may have been protective in cold ischemia and reperfusion in an investigation by Chen and colleagues (166). Induced heat shock protein 70 may affect the Bcl-xL level, which seems to be involved in the reduction of liver damage (167). Intracellular heat shock protein has been found to be directly hepatoprotective, but Kuboki and colleagues showed that extracellular heat shock protein was not a significant contributor to hepatoprotection (168). Recent evidence has demonstrated that extracellular

heat shock protein 72 binds to toll-like receptors 2 and 4, which then signal through nuclear factor-kappa beta to increase macrophage inflammatory protein 2 production. According to Galloway and colleagues, the time at which heat shock protein 72 is available to hepatocytes may determine the overall effect of that protein on the response to injury (169).

Erythropoietin

Erythropoietin is involved in more than just erythropoiesis. Interest in the cytoprotective features of this glycoprotein hormone is increasing at an almost exponential rate (170). Erythropoietin may have potential benefits for patients with any of a wide variety of disorders (Alzheimer disease, cardiac insufficiency, stroke, trauma, complications of diabetes) (171). The potential neuroprotective and cardioprotective roles of erythropoietin (independent of its hematopoietic action) against ischemia have also been documented (10).

Research has suggested that erythropoietin is effective in reducing hepatic ischemia-reperfusion injury and that the preischemic administration of erythropoietin exerts a protective effect (172). In a study by Hochhauser and colleagues, pretreatment with 1 dose of recombinant human erythropoietin attenuated postischemia-reperfusion hepatocyte apoptotic damage, and the modulation of nuclear factor-kappa beta and c-Jun N-terminal kinase may have had a role in those protective effects (173). When recombinant human erythropoietin was administered 5 minutes before ischemia in a study by Sepodes and colleagues, biochemical evidence of liver injury was reduced, but that effect was not noted when recombinant human erythropoietin was administered 5 minutes before reperfusion (174). In a model of warm hepatic ischemia and reperfusion, the data suggested a protective effect from erythropoietin administration and showed that the results of intraportal venous injection were superior to those of subcutaneous preconditioning (175). In fetal rats, administration of recombinant human erythropoietin-reduced thiobarbituric acid-reactive substances induced lipid peroxidation (176).

Noting that recombinant human erythropoietin had been studied in liver ischemia, but not in hepatic resection and regeneration, Schmeding and colleagues showed that recombinant human erythropoietin increased liver regeneration in rats after a 70% liver resection and enhanced survival in that model after a 90% hepatectomy (177). Both erythropoietin and mitochondrial potassium channel openers have exerted protective effects in liver ischemia-reperfusion injury. Yazihan and colleagues found that the potassium channel inhibitor glibenclamide reduced the protective effects of erythropoietin during hydrogen peroxide toxicity in hepatocytes (178). In a study of laparoscopically induced oxidative injury, preischemic administration of erythropoietin decreased oxidative injury, but not as much as laparoscopic preconditioning (179).

Further studies of the role of erythropoietin in various cytoprotective processes, including liver ischemia-reperfusion injury, will clarify the dynamic effects of this important mediator.

Selectins

Selectins are cellular adhesion molecules. During ischemia and reperfusion injury, they are involved in both cellular infiltration and molecular signaling (180). There are 3 types of selectins: E, L, and P. With respect to leukocyte recruitment into inflamed liver sinusoids, selectins are not required in all instances, but they are required in ischemia and reperfusion (181). Investigators have found that interfering with P-selectin produces a protective effect against liver ischemia reperfusion injury. In a study of warm ischemia and reperfusion by Khandoga and colleagues, P-selectin deficiency prevented microvascular injury and apoptosis (182). Blocking the P-selectin glycoprotein ligand-1 with an antibody has been shown to be a simple and effective strategy for protecting against ischemia reperfusion injury in models of cold ischemia liver transplant (183). The recombinant P-selectin glycoprotein ligand-1 immunoglobulin blockade of CD-62-mediated adhesive interactions reduced ischemia-reperfusion injury in steatotic rat livers in an investigation by Amersi and colleagues (184). The addition of a lipid-soluble iron chelator substantially increased the protection provided by recombinant P-selectin glycoprotein ligand-1 immunoglobulin alone, as demonstrated by Amersi and colleagues in another study (185). Dendritic cells may have an important role in hepatic or renal ischemia-reperfusion injury, and anti-P-selectin lectin-epidermal growth factor domain monoclonal antibody may inhibit local dendritic cell migration and accumulation (186). In cases of uncontrolled hemorrhagic shock, the

blockade of L-selectin has been associated with decreased hepatocellular injury and increased survival (187). Some authors have suggested that the improved hemodynamics and decreased leukocyte adherence occurring after treatment with N-acetylcysteine might result from the shedding of selectins (188).

In some models of hepatic ischemia and reperfusion, hepatocellular injury was independent of P-selectin and intercellular adhesion molecule-1 (189). It has been suggested that because of compensation by uninhibited cell-adhesion molecules, treatments that target only a single selectin can be ineffective (180). Protective results, including a significant decrease in the level of serum tumor necrosis factor α, an equally significant increase in the level of serum-protective IL-10 (190), and an increase in the modulation of protein kinases and chemokines (191), have been reported after treatment with the multiselectin blocker Texas Biotechnology Corporation (TBC)-1269. In addition, the multiselectin inhibitor OC-229 provided both functional and histologic protection of the ischemic liver, including dissociation of nuclear factor kappa beta and activator protein 1 activity, with a reduction in the activity of activator protein 1 and an increment in nuclear factory kappa beta activation. (192).

Protein Kinases

We will now consider some of the literature pertaining to the role of protein kinases in liver ischemia-reperfusion injury. A mitogen-activated protein kinase, c-Jun N-terminal kinase, has been reported to have a role in the mechanism of ischemia-reperfusion injury (193). Dysregulated c-Jun N-terminal kinase signaling is also believed to contribute to many other disorders, including those involving neurodegeneration, chronic inflammation, birth defects, and cancer (11). It has been suggested that the generation of reactive oxygen species during hypoxia directly activates c-Jun N-terminal kinase in a Rac-1-dependent process (194). c-Jun N-terminal kinase inhibitors were shown to exert protective effects in liver ischemia and reperfusion and were associated with decreased necrosis and apoptosis (195, 196). Tacrolimus (FK506) also reduced ischemia-reperfusion–induced apoptosis and necrosis, including reduced c-Jun N-terminal kinase 1/stress-activated protein kinase 1 and caspase 3 activation (197). Lee and associates showed that c-Jun N-terminal kinase inhibitors exacerbated hepatic ischemia-reperfusion injury (198). Those authors acknowledged that their results differed from the findings of other studies, and while they could not provide a definitive explanation for the discrepancy, they cited possible differences in dosing schedules as a potential explanation.

Other mitogen-activated protein kinases have been studied in addition to c-Jun N-terminal kinase. In a study by Zhao and colleagues, fingolimod decreased ischemia-reperfusion injury by activating Akt signaling and down-regulating the mitogen-activated protein kinase pathway (199), which led to the down-regulation of early growth response-1 (200). The inhibition of p38 has been shown to produce protective effects (201). In 2007, Kobayashi and colleagues reported on the beneficial effects of p38 activation, but stated that the role of mitogen-activated protein kinase is controversial and depends on several factors (202). Investigations have considered the small GTPase Rho and the effector Rho kinase. In studies of Rho inhibitors, protective effects such as a reduction in the generation of reactive oxygen species and the suppressed release of inflammatory cytokines (203), the amelioration of postischemic microcirculation (204), the suppression of polymorphonuclear leukocytes and inflammatory cytokines (205), prolonged survival (206), inhibited contraction of hepatic stellate cells (207), and reduced damage in carbon tetrachloride-induced injury (208) have been reported. In hepatocytes, the adenoviral-mediated overexpression of double-negative Rho kinase has been shown to suppress the production of reactive oxygen species and the release of proinflammatory cytokines, and to significantly prolong survival (209).

Matrix Metalloproteinases

The matrix metalloproteinases are zinc-dependent endopeptidases. The 24 human matrix metallo-proteinases are one of the major families of proteinases that have an important role in the responses of cells to their microenvironment, including the combined ability to degrade all components of the extracellular matrix (210).

Studies have shown that matrix metallo-proteinases have an important role in liver ischemia-reperfusion injury, and remaining challenges include

defining their mechanism of activation and targets (211). By altering the extracellular matrix, matrix metalloproteinases also have a major role in cold ischemia- warm reperfusion injury. Therefore, their inhibition might be a new strategy for improving preservation solutions (212). Because matrix metalloproteinases and their tissue inhibitors are released and activated during ischemia and reperfusion, the imbalance of those substances has been shown to contribute to the fibrosis that can occur after liver injury (12). The therapeutic effects of inhibiting matrix metalloproteinases have been documented in histologic studies and analyses of serum hepatic enzyme levels (213) and shown in the inhibition of gelatinolytic activity and the decreased release of inflammatory cytokines (214). In a study by Chen and colleagues, reperfusion injury induced an increase in the level of matrix metalloproteinase-9, and oxygen radical production was implicated in matrix metalloproteinase expression and liver injury (215). In humans, only matrix metalloproteinase-9 seems to be involved in ischemia-reperfusion injury during liver transplant, and nonserine-protease/plasmin pathways have been shown to be involved in matrix metalloproteinase regulation (216). In another study in human subjects, matrix metalloproteinase-2 and matrix metalloproteinase-9 were not associated with the late phase of liver ischemia-reperfusion injury (217).

In steatotic liver grafts, T cells, monocytes, and macrophages have been defined as the main sources of matrix metalloproteinase-9, the up-regulation of which has been associated with impaired liver function (218). Matrix metalloproteinase-9–specific inhibition is a critical element in leukocyte recruitment and activation; this suggests that matrix metalloproteinase-9 inhibition is a potential therapeutic target (219). In another report, matrix metalloproteinase-9 blockade was associated with the attenuation of tumor necrosis factor α release and endothelial CD62P expression, which improved postischemic survival (220).

Cytokines and Chemokines

Cytokines and chemokines, which are important mediators of hepatic ischemia-reperfusion injury, produce both harmful and beneficial effects. In ischemia and reperfusion, chemokines reportedly influence the activity of neutrophils, macrophages, and T cells (221). The CXC chemokine ligand 10 regulated liver inflammation in a study in which CXC chemokine ligand 10 knockout mice sustained less hepatic injury (13). Involvement of IL-1 and its receptor in the induction of inducible nitric oxide synthase was previously discussed in this review (46-48), and gene delivery of the IL-1 receptor was potentially helpful in reducing ischemia-reperfusion injury after transplant in a study by Harada and colleagues (222). Data have shown that the interferon type 1 (but not type 2) pathway is required for ischemia-reperfusion–triggered liver inflammation and damage (223).

IL-12 facilitates cell-mediated cytotoxicity. Dimaprit, a histamine agonist, was shown to exert protective effects, possibly by decreasing the level of released IL-12 (224), and the proinflammatory effects of IL-12 have been found to be independent of signal transducer and activation of transcription 4 (STAT-4) (225). A dual inhibitor of IL-1 and tumor necrosis factor α decreased liver injury in a study by Takiguchi and colleagues (226), and Ben-Ari and colleagues showed that monoclonal antibodies against tumor necrosis factor α attenuated postischemic injury (especially apoptosis) (227). The suppression of tumor necrosis factor α has also been identified as a possible protective mechanism in ischemic preconditioning (108). IL-18 was found to suppress anti-inflammatory cytokines during hepatic ischemia-reperfusion injury (228). Tumor necrosis factor α exerts pleiotropic effects on the liver. In a transplant model, Conzelmann and colleagues showed that the graft tumor necrosis factor receptor-1 decreased graft injury and recipient tumor necrosis factor receptor-1 increased injury (229).

Cytokines also exert beneficial effects. Guidi and colleagues found that during ischemia, IL-6 levels were significantly increased (230), and IL-6 has been implicated as a likely mediator of protective effects during ischemic preconditioning (105,106). The adenoviral-based gene transfer of IL-10 has been shown to protect the liver (231), and in studies by Ke and colleagues (232) and Oreopoulos and colleagues (233), hypertonic saline solution attenuated hepatic ischemia and reperfusion injury by increasing the release of IL-10. Kawakami and colleagues showed that recombinant human IL-11 protects against carbon tetrachloride-induced liver injury by heme oxygenase-1 induction (234), and Kato and colleagues demonstrated that IL-13 exerts prominent

protective effects for hepatocytes and endothelial cells (235).

Conclusion

Although the complex pathways involved in hepatic ischemia-reperfusion injury have yet to be completely elucidated, much progress has been made in recent years. Past, current, and future investigations of reactive oxygen species, toll-like receptors, leukocyte-endothelial interactions, the heme oxygenase system, nitric oxide, and other molecules listed in this review are crucial to understanding the roles of those mediators and their interactions. More extensive studies of ischemic preconditioning are warranted, because some of those conducted to date have not been as successful as expected. The definitive management of liver ischemia-reperfusion injury has not been established, even though multiple downstream pathways and well-identified cascades are already known. In future investigations, a greater understanding of all factors involved will enable more effective treatment for liver ischemia-reperfusion injury.

References

1. Vardanian AJ, Busuttil RW, Kupiec-Weglinski JW. Molecular mediators of liver ischemia and reperfusion injury: a brief review. Mol Med. 2008;14(5-6):337-345.
2. Montalvo-Jave EE, Escalante-Tattersfield T, Ortega-Salgado JA, Piña E, Geller DA. Factors in the pathophysiology of the liver ischemia-reperfusion injury. J Surg Res. 2008;147(1):153-159.
3. Wink DA, Miranda KM, Espey MG, et al. Mechanisms of the antioxidant effects of nitric oxide. Antioxid Redox Signal. 2001;3(2):203-213.
4. Chen T, Zamora R, Zuckerbraun B, Billiar TR. Role of nitric oxide in liver injury. Curr Mol Med. 2003;3(6):519-526.
5. Albrecht EW, Stegeman CA, Heeringa P, Henning RH, van Goor H. Protective role of endothelial nitric oxide synthase. J Pathol. 2003;199(1):8-17.
6. Gurusamy KS, Kumar Y, Sharma D, Davidson BR. Ischaemic preconditioning for liver transplantation. Cochrane Database Syst Rev. 2008;Jan 23(1):CD006315.
7. Caldwell CC, Tschoep J, Lentsch AB. Lymphocyte function during hepatic ischemia/reperfusion injury. J Leukoc Biol. 2007;82(3):457-464.
8. Huang Y, Rabb H, Womer KL. Ischemia-reperfusion and immediate T cell responses. Cell Immunol. 2007;248(1):4-11.
9. Ferrándiz ML, Devesa I. Inducers of heme oxygenase-1. Curr Pharm Des. 2008;14(5):473-486.
10. Joyeux-Faure M. Cellular protection by erythropoietin: new therapeutic implications? J Pharmacol Exp Ther. 2007;323(3):759-762.
11. Johnson GL, Nakamura K. The c-jun kinase/stress-activated pathway: regulation, function and role in human disease. Biochim Biophys Acta. 2007;1773(8):1341-1348.
12. Viappiani S, Sariahmetoglu M, Schulz R. The role of matrix metalloproteinase inhibitors in ischemia-reperfusion injury in the liver. Curr Pharm Des. 2006;12(23):2923-2934.
13. Zhai Y, Shen XD, Gao F, et al. CXCL10 regulates liver innate immune response against ischemia and reperfusion injury. Hepatology. 2008;47(1):207-214.
14. Zhang W, Wang M, Xie HY, et al. Role of reactive oxygen species in mediating hepatic ischemia-reperfusion injury and its therapeutic applications in liver transplantation. Transplant Proc. 2007;39(5):1332-1337.
15. Harada H, Hines IN, Flores S, et al. Role of NADPH oxidase-derived superoxide in reduced size liver ischemia and reperfusion injury. Arch Biochem Biophys. 2004;423(1):103-108.
16. Fukai M, Hayashi T, Yokota R, et al. Lipid peroxidation during ischemia depends on ischemia time in warm ischemia and reperfusion of rat liver. Free Radic Biol Med. 2005;38(10):1372-1381.
17. Boin Ide F, Silva Ode C, Souza ME, Santos AC, Leonardi LS. Pyruvate kinase activation and lipoperoxidation after selective hepatic ischemia in Wistar rats. Acta Cir Bras. 2006;21(suppl 1):19-23.
18. Wheeler MD, Katuna M, Smutney OM, et al. Comparison of the effect of adenoviral delivery of three superoxide dismutase genes against hepatic ischemia-reperfusion injury. Hum Gene Ther. 2001;12(18):2167-2177.
19. Wheeler MD, Nakagami M, Bradford BU, et al. Overexpression of manganese superoxide dismutase prevents alcohol-induced liver injury in the rat. J Biol Chem. 2001;276(39):36664-36672.
20. Lehmann TG, Luedde T, Schwabe RF, et al. Minimizing oxidative stress by gene delivery of superoxide dismutase accelerates regeneration after transplantation of reduced-size livers in the rat. Liver Transpl. 2006 ;12(4):550-559.
21. Lehmann TG, Wheeler MD, Froh M, et al. Effects of three superoxide dismutase genes delivered with an adenovirus on graft function after transplantation of fatty livers in the rat. Transplantation. 2003;76(1):28-37.
22. Hiranuma S, Ito K, Noda Y, Ozasa H, Koike Y, Horikawa S. Amelioration of hepatic ischemia/reperfusion injury in the remnant liver after partial hepatectomy in rats. J Gastroenterol Hepatol. 2007;22(12):2167-2172.
23. Nakamoto N, Tada S, Kameyama K, et al. A free radical scavenger, edaravone, attenuates steatosis and cell death via reducing inflammatory cytokine production in rat acute liver injury. Free Radic Res. 2003;37(8):849-859.
24. Taniguchi M, Uchinami M, Doi K, et al. Edaravone reduces ischemia-reperfusion injury mediators in rat liver. J Surg Res. 2007;137(1):69-74.
25. Ninomiya M, Shimada M, Harada N, et al. Beneficial effect of MCI-186 on hepatic warm ischemia-reperfusion in the rat. Transplantation. 2002;74(10):1470-1472.
26. Ninomiya M, Shimada M, Harada N, Soejima Y, Suehiro T, Maehara Y. The hydroxyl radical scavenger MCI-186 protects the liver from experimental cold ischaemia-reperfusion injury. Br J Surg. 2004;91(2):184-190.
27. Sener G, Sehirli O, Ercan F, Sirvanci S, Gedik N, Kacmaz A. Protective effect of MESNA (2-mercaptoethane sulfonate) against hepatic ischemia/reperfusion injury in rats. Surg Today. 2005;35(7):575-580.
28. Sener G, Kabasakal L, Sehirli O, Ercan F, Gedik N. 2-Mercaptoethane sulfonate (MESNA) protects against biliary obstruction-induced oxidative damage in rats. Hepatol Res. 2006;35(2):140-146.
29. Bi W, Cai J, Xue P, et al. Protective effect of nitronyl nitroxide-amino acid conjugates on liver ischemia-reperfusion induced injury in rats. Bioorg Med Chem Lett. 2008;18(6):1788-1794.
30. Dulundu E, Ozel Y, Topaloglu U, et al. Alpha-lipoic acid protects against hepatic ischemia-reperfusion injury in rats. Pharmacology. 2007;79(3):163-170.
31. Tselepidis S, Papazoglou L, Dessiris A, et al. Liver injury after ischemia and reperfusion: the role of oxygen free radicals. Mil Med. 2004;169(7):531-535.
32. Wu TJ, Khoo NH, Zhou F, Day BJ, Parks DA. Decreased hepatic ischemia-reperfusion injury by manganese-porphyrin complexes. Free Radic Res. 2007;41(2):127-134.
33. Park SW, Choi SM, Lee SM. Effect of melatonin on altered expression of vasoregulatory genes during hepatic ischemia/reperfusion. Arch Pharm Res. 2007;30(12):1619-1624.

34. Chen JC, Ng CJ, Chiu TF, Chen HM. Altered neutrophil apoptosis activity is reversed by melatonin in liver ischemia-reperfusion. J Pineal Res. 2003;34(4):260-264.
35. Liang R, Nickkholgh A, Hoffmann K, et al. Melatonin protects from hepatic reperfusion injury through inhibition of IKK and JNK pathways and modification of cell proliferation. J Pineal Res. 2009;46(1):8-14.
36. Kim SH, Lee SM. Cytoprotective effects of melatonin against necrosis and apoptosis induced by ischemia/reperfusion injury in rat liver. J Pineal Res. 2008;44(2):165-171.
37. Okatani Y, Wakatsuki A, Reiter RJ, Enzan H, Miyahara Y. Protective effect of melatonin against mitochondrial injury induced by ischemia and reperfusion of rat liver. Eur J Pharmacol. 2003;469(1-3):145-152.
38. Zhang WH, Li JY, Zhou Y. Melatonin abates liver ischemia/reperfusion injury by improving the balance between nitric oxide and endothelin. Hepatobiliary Pancreat Dis Int. 2006;5(4):574-579.
39. Rodríguez-Reynoso S, Leal C, Portilla E, Olivares N, Muñiz J. Effect of exogenous melatonin on hepatic energetic status during ischemia/reperfusion: possible role of tumor necrosis factor-alpha and nitric oxide. J Surg Res. 2001;100(2):141-149.
40. Mathes AM, Kubulus D, Weiler J, et al. Melatonin receptors mediate improvements of liver function but not of hepatic perfusion and integrity after hemorrhagic shock in rats. Crit Care Med. 2008;36(1):24-29.
41. Baykara B, Tekmen I, Pekcetin C, et al. The protective effects of carnosine and melatonin in ischemia-reperfusion injury in the rat liver. Acta Histochem. 2009;111(1):42-51.
42. Sener G, Tosun O, Sehirli AO, et al. Melatonin and N-acetylcysteine have beneficial effects during hepatic ischemia and reperfusion. Life Sci. 2003;72(24):2707-2718.
43. Bülbüller N, Cetinkaya Z, Akkus MA, et al. The effects of melatonin and prostaglandin E1 analogue on experimental hepatic ischaemia reperfusion damage. Int J Clin Pract. 2003;57(10):857-860.
44. Kirimlioglu H, Ecevit A, Yilmaz S, Kirimlioglu V, Karabulut AB. Effect of resveratrol and melatonin on oxidative stress enzymes, regeneration, and hepatocyte ultrastructure in rats subjected to 70% partial hepatectomy. Transplant Proc. 2008;40(1):285-289.
45. Stuehr DJ. Enzymes of the L-arginine to nitric oxide pathway. J Nutr. 2004;134(10 suppl):2748S-2751S; discussion 2765S-2767S.
46. Yanagida H, Kaibori M, Yamada M, et al. Induction of inducible nitric oxide synthase in hepatocytes isolated from rats with ischemia-reperfusion injury. Transplant Proc. 2004;36(7):1962-1964.
47. Yanagida H, Kaibori M, Yoshida H, et al. Hepatic ischemia/reperfusion upregulates the susceptibility of hepatocytes to confer the induction of inducible nitric oxide synthase gene expression. Shock. 2006;26(2):162-168.
48. Teshima S, Nakanishi H, Nishizawa M, et al. Up-regulation of IL-1 receptor through PI3K/Akt is essential for the induction of iNOS gene expression in hepatocytes. J Hepatol. 2004;40(4):616-623.
49. Hines IN, Harada H, Flores S, Gao B, McCord JM, Grisham MB. Endothelial nitric oxide synthase protects the post-ischemic liver: potential interactions with superoxide. Biomed Pharmacother. 2005;59(4):183-189.
50. Lin HI, Wang D, Leu FJ, Chen CF, Chen HI. Ischemia and reperfusion of liver induces eNOS and iNOS expression: effects of a NO donor and NOS inhibitor. Chin J Physiol. 2004;47(3):121-127.
51. Hines IN, Kawachi S, Harada H, et al. Role of nitric oxide in liver ischemia and reperfusion injury. Mol Cell Biochem. 2002;234-235(1-2):229-237.
52. Koti RS, Tsui J, Lobos E, Yang W, Seifalian AM, Davidson BR. Nitric oxide synthase distribution and expression with ischemic preconditioning of the rat liver. FASEB J. 2005;19(9):1155-1157.
53. Theruvath TP, Zhong Z, Currin RT, Ramshesh VK, Lemasters JJ. Endothelial nitric oxide synthase protects transplanted mouse livers against storage/reperfusion injury: Role of vasodilatory and innate immunity pathways. Transplant Proc. 2006;38(10):3351-3357.
54. Serracino-Inglott F, Virlos IT, Habib NA, Williamson RC, Mathie RT. Differential nitric oxide synthase expression during hepatic ischemia-reperfusion. Am J Surg. 2003;185(6):589-595.
55. Taniai H, Hines IN, Bharwani S, et al. Susceptibility of murine periportal hepatocytes to hypoxia-reoxygenation: role for NO and Kupffer cell-derived oxidants. Hepatology. 2004;39(6):1544-1552.
56. Wang LM, Tian XF, Song QY, Gao ZM, Luo FW, Yang CM. Expression and role of inducible nitric oxide synthase in ischemia-reperfusion liver in rats. Hepatobiliary Pancreat Dis Int. 2003;2(2):252-258.
57. Kimura H, Katsuramaki T, Isobe M, et al. Role of inducible nitric oxide synthase in pig liver transplantation. J Surg Res. 2003;111(1):28-37.
58. Takamatsu Y, Shimada K, Yamaguchi K, Kuroki S, Chijiiwa K, Tanaka M. Inhibition of inducible nitric oxide synthase prevents hepatic, but not pulmonary, injury following ischemia-reperfusion of rat liver. Dig Dis Sci. 2006;51(3):571-579.
59. Meguro M, Katsuramaki T, Nagayama M, et al. A novel inhibitor of inducible nitric oxide synthase (ONO-1714) prevents critical warm ischemia-reperfusion injury in the pig liver. Transplantation. 2002;73(9):1439-1446.
60. Tsuchihashi S, Kaldas F, Chida N, et al. FK330, a novel inducible nitric oxide synthase inhibitor, prevents ischemia and reperfusion injury in rat liver transplantation. Am J Transplant. 2006;6(9):2013-2022.
61. Lee VG, Johnson ML, Baust J, Laubach VE, Watkins SC, Billiar TR. The roles of iNOS in liver ischemia-reperfusion injury. Shock. 2001;16(5):355-360.
62. Kurabayashi M, Takeyoshi I, Yoshinari D, et al. NO donor ameliorates ischemia-reperfusion injury of the rat liver with iNOS attenuation. J Invest Surg. 2005;18(4):193-200.
63. Yaylak F, Canbaz H, Caglikulekci M, et al. Liver tissue inducible nitric oxide synthase (iNOS) expression and lipid peroxidation in experimental hepatic ischemia reperfusion injury stimulated with lipopolysaccharide: the role of aminoguanidine. J Surg Res. 2008;148(2):214-223.
64. Carlucci F, Marinello E, Rosi F, et al. Nitric oxide generation is associated with an unbalance of protein tyrosine phosphatases during liver transplantation. Biomed Pharmacother. 2007;61(4):216-221.
65. Koeppel TA, Mihaljevic N, Kraenzlin B, et al. Enhanced iNOS gene expression in the steatotic rat liver after normothermic ischemia. Eur Surg Res. 2007;39(5):303-311.
66. Jeyabalan G, Klune JR, Nakao A, et al. Arginase blockade protects against hepatic damage in warm ischemia-reperfusion. Nitric Oxide. 2008;19(1):29-35.
67. Kaizu T, Ikeda A, Nakao A, et al. Donor graft adenoviral iNOS gene transfer ameliorates rat liver transplant preservation injury and improves survival. Hepatology. 2006;43(3):464-473.
68. Hsu CM, Wang JS, Liu CH, Chen LW. Kupffer cells protect liver from ischemia-reperfusion injury by an inducible nitric oxide synthase-dependent mechanism. Shock. 2002;17(4):280-285.
69. Aram G, Potter JJ, Liu X, Torbenson MS, Mezey E. Lack of inducible nitric oxide synthase leads to increased hepatic apoptosis and decreased fibrosis in mice after chronic carbon tetrachloride administration. Hepatology. 2008;47(6):2051-2058.
70. Hines IN, Harada H, Bharwani S, Pavlick KP, Hoffman JM, Grisham MB. Enhanced post-ischemic liver injury in iNOS-deficient mice: a cautionary note. Biochem Biophys Res Commun. 2001 22;284(4):972-976.
71. Rivera-Chavez FA, Toledo-Pereyra LH, Dean RE, Crouch L, Ward PA. Exogenous and endogenous nitric oxide but not iNOS inhibition improves function and survival of ischemically injured livers. J Invest Surg. 2001;14(5):267-273.
72. Lu P, Liu F, Yao Z, et al. Nitrite-derived nitric oxide by xanthine oxidoreductase protects the liver against ischemia-reperfusion injury. Hepatobiliary Pancreat Dis Int. 2005;4(3):350-355.
73. Von Knethen A, Brüne B. Activation of peroxisome proliferator-activated receptor gamma by nitric oxide in monocytes/macrophages down-regulates p47phox and attenuates the respiratory burst. J Immunol. 2002;169(5):2619-2626.
74. Crosby MB, Svenson J, Gilkeson GS, Nowling TK. A novel PPAR response element in the murine iNOS promoter. Mol Immunol. 2005;42(11):1303-1310.

75. Crosby MB, Svenson JL, Zhang J, Nicol CJ, Gonzalez FJ, Gilkeson GS. Peroxisome proliferation-activated receptor (PPAR)gamma is not necessary for synthetic PPARgamma agonist inhibition of inducible nitric-oxide synthase and nitric oxide. J Pharmacol Exp Ther. 2005;312(1):69-76.
76. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol. 2003;21:335-376.
77. Hopkins PA, Sriskandan S. Mammalian Toll-like receptors: to immunity and beyond. Clin Exp Immunol. 2005;140(3):395-407.
78. Jin X, Wang L, Wu HS, et al. N-acetylcysteine inhibits activation of toll-like receptor 2 and 4 gene expression in the liver and lung after partial hepatic ischemia-reperfusion injury in mice. Hepatobiliary Pancreat Dis Int. 2007;6(3):284-289.
79. Zhang JX, Wu HS, Wang H, Zhang JH, Wang Y, Zheng QC. Protection against hepatic ischemia/reperfusion injury via downregulation of toll-like receptor 2 expression by inhibition of Kupffer cell function. World J Gastroenterol. 2005;11(28):4423-4426.
80. Prince JM, Levy RM, Yang R, et al. Toll-like receptor-4 signaling mediates hepatic injury and systemic inflammation in hemorrhagic shock. J Am Coll Surg. 2006;202(3):407-417.
81. Zhai Y, Shen XD, O'Connell R, et al. Cutting edge: TLR4 activation mediates liver ischemia/reperfusion inflammatory response via IFN regulatory factor 3-dependent MyD88-independent pathway. J Immunol. 2004;173(12):7115-7119.
82. Shen XD, Ke B, Zhai Y, et al. Absence of toll-like receptor 4 (TLR4) signaling in the donor organ reduces ischemia and reperfusion injury in a murine liver transplantation model. Liver Transpl. 2007;13(10):1435-1443.
83. Wang H, Li ZY, Wu HS, et al. Endogenous danger signals trigger hepatic ischemia/reperfusion injury through toll-like receptor 4/nuclear factor-kappa B pathway. Chin Med J (Engl). 2007;120(6):509-514.
84. Yin H, Huang BJ, Yang H, et al. Pretreatment with soluble ST2 reduces warm hepatic ischemia/reperfusion injury. Biochem Biophys Res Commun. 2006;351(4):940-946.
85. Wang L, Xu JB, Wu HS, et al. The relationship between activation of TLR4 and partial hepatic ischemia/reperfusion injury in mice. Hepatobiliary Pancreat Dis Int. 2006;5(1):101-104.
86. Peng Y, Gong JP, Liu CA, Li XH, Gan L, Li SB. Expression of toll-like receptor 4 and MD-2 gene and protein in Kupffer cells after ischemia-reperfusion in rat liver graft. World J Gastroenterol. 2004;10(19):2890-2893.
87. Wu HS, Zhang JX, Wang L, Tian Y, Wang H, Rotstein O. Toll-like receptor 4 involvement in hepatic ischemia/reperfusion injury in mice. Hepatobiliary Pancreat Dis Int. 2004;3(2):250-253.
88. Hua J, Qiu de K, Li JQ, Li EL, Chen XY, Peng YS. Expression of Toll-like receptor 4 in rat liver during the course of carbon tetrachloride-induced liver injury. J Gastroenterol Hepatol. 2007;22(6):862-869.
89. Tsung A, Hoffman RA, Izuishi K, et al. Hepatic ischemia/reperfusion injury involves functional TLR4 signaling in nonparenchymal cells. J Immunol. 2005;175(11):7661-7668.
90. Tsung A, Sahai R, Tanaka H, et al. The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion. J Exp Med. 2005;201(7):1135-1143.
91. Tsung A, Klune JR, Zhang X, et al. HMGB1 release induced by liver ischemia involves Toll-like receptor 4 dependent reactive oxygen species production and calcium-mediated signaling. J Exp Med. 2007;204(12):2913-2923.
92. DeOliveira ML, Graf R, Clavien PA. Ischemic preconditioning: promises from the laboratory to patients–sustained or disillusioned? Am J Transplant. 2008;8(3):489-491.
93. Koneru B, Shareef A, Dikdan G, et al. The ischemic preconditioning paradox in deceased donor liver transplantation-evidence from a prospective randomized single blind clinical trial. Am J Transplant. 2007;7(12):2788-2796.
94. Funaki H, Shimizu K, Harada S, et al. Essential role for nuclear factor kappaB in ischemic preconditioning for ischemia-reperfusion injury of the mouse liver. Transplantation. 2002;74(4):551-556.
95. Heizmann O, Loehe F, Volk A, Schauer RJ. Ischemic preconditioning improves postoperative outcome after liver resections: a randomized controlled study. Eur J Med Res. 2008;13(2):79-86.
96. Jang JH, Kang KJ, Kang Y, Lee IS, Graf R, Clavien PA. Ischemic preconditioning and intermittent clamping confer protection against ischemic injury in the cirrhotic mouse liver. Liver Transpl. 2008;14(7):980-988.
97. Saidi RF, Chang J, Brooks S, Nalbantoglu I, Adsay V, Jacobs MJ. Ischemic preconditioning and intermittent clamping increase the tolerance of fatty liver to hepatic ischemia-reperfusion injury in the rat. Transplant Proc. 2007;39(10):3010-3014.
98. Amador A, Grande L, Martí J, et al. Ischemic pre-conditioning in deceased donor liver transplantation: a prospective randomized clinical trial. Am J Transplant. 2007;7(9):2180-2189.
99. Jassem W, Fuggle SV, Cerundolo L, Heaton ND, Rela M. Ischemic preconditioning of cadaver donor livers protects allografts following transplantation. Transplantation. 2006;81(2):169-174.
100. Lee WY, Lee SM. Ischemic preconditioning protects post-ischemic oxidative damage to mitochondria in rat liver. Shock. 2005;24(4):370-375.
101. Arai M, Tejima K, Ikeda H, et al. Ischemic preconditioning in liver pathophysiology. J Gastroenterol Hepatol. 2007;22(suppl 1):S65-S67.
102. Choukèr A, Martignoni A, Schauer RJ, et al. Ischemic preconditioning attenuates portal venous plasma concentrations of purines following warm liver ischemia in man. Eur Surg Res. 2005;37(3):144-152.
103. Schauer RJ, Gerbes AL, Vonier D, op den Winkel M, Fraunberger P, Bilzer M. Induction of cellular resistance against Kupffer cell-derived oxidant stress: a novel concept of hepatoprotection by ischemic preconditioning. Hepatology. 2003;37(2):286-295.
104. Choukèr A, Martignoni A, Schauer R, et al. Beneficial effects of ischemic preconditioning in patients undergoing hepatectomy: the role of neutrophils. Arch Surg. 2005;140(2):129-136.
105. Teoh N, Field J, Farrell G. Interleukin-6 is a key mediator of the hepatoprotective and pro-proliferative effects of ischaemic preconditioning in mice. J Hepatol. 2006;45(1):20-27.
106. Matsumoto T, O'Malley K, Efron PA, et al. Interleukin-6 and STAT3 protect the liver from hepatic ischemia and reperfusion injury during ischemic preconditioning. Surgery. 2006;140(5):793-802.
107. Iñiguez M, Berasain C, Martinez-Ansó E, et al. Cardiotrophin-1 defends the liver against ischemia-reperfusion injury and mediates the protective effect of ischemic preconditioning. J Exp Med. 2006;203(13):2809-2815.
108. Shinoda M, Shimazu M, Wakabayashi G, Tanabe M, Hoshino K, Kitajima M. Tumor necrosis factor suppression and microcirculatory disturbance amelioration in ischemia/reperfusion injury of rat liver after ischemic preconditioning. J Gastroenterol Hepatol. 2002;17(11):1211-1219.
109. Massip-Salcedo M, Casillas-Ramirez A, Franco-Gou R, et al. Heat shock proteins and mitogen-activated protein kinases in steatotic livers undergoing ischemia-reperfusion: some answers. Am J Pathol. 2006;168(5):1474-1485.
110. Ricciardi R, Schaffer BK, Kim RD, et al. Protective effects of ischemic preconditioning on the cold-preserved liver are tyrosine kinase dependent. Transplantation. 2001;72(3):406-412.
111. Ricciardi R, Meyers WC, Schaffer BK, et al. Protein kinase C inhibition abrogates hepatic ischemic preconditioning responses. J Surg Res. 2001;97(2):144-149.
112. Ricciardi R, Shah SA, Wheeler SM, et al. Regulation of NFkappaB in hepatic ischemic preconditioning. J Am Coll Surg. 2002;195(3):319-326.
113. Sahin DA, Haliloglu B, Sahin FK, et al. Stepwise rising CO2 insufflation as an ischemic preconditioning method. J Laparoendosc Adv Surg Tech A. 2007;17(6):723-729.
114. Jang JH, Moritz W, Graf R, Clavien PA. Preconditioning with death ligands FasL and TNF-alpha protects the cirrhotic mouse liver against ischaemic injury. Gut. 2008;57(4):492-499. Erratum in: Gut. 2008;57(9):1340.
115. Lü H, Yang LQ, Yu WF, et al. [Protection of liver against ischemia/reperfusion injury by Kupffer cell mediated emulsified isoflurane preconditioning: experiment with rats] Zhonghua Yi Xue Za Zhi. 2007;87(35):2468-2471. Chinese.

116. Izuishi K, Tsung A, Jeyabalan G, et al. Cutting edge: high-mobility group box 1 preconditioning protects against liver ischemia-reperfusion injury. J Immunol. 2006;176(12):7154-7158.
117. Van As AB, Foroutan HR, Lotz Z, Tyler M, Millar AJ, Kahn D. Ischaemic preconditioning of the liver before transplantation. S Afr J Surg. 2007;45(4):122-124, 126.
118. Azoulay D, Del Gaudio M, Andreani P, et al. Effects of 10 minutes of ischemic preconditioning of the cadaveric liver on the graft's preservation and function: the ying and the yang. Ann Surg. 2005;242(1):133-139.
119. Caldwell CC, Okaya T, Martignoni A, Husted T, Schuster R, Lentsch AB. Divergent functions of CD4+ T lymphocytes in acute liver inflammation and injury after ischemia-reperfusion. Am J Physiol Gastrointest Liver Physiol. 2005;289(5):G969-G976.
120. Zhai Y, Shen XD, Hancock WW, et al. CXCR3+CD4+ T cells mediate innate immune function in the pathophysiology of liver ischemia/reperfusion injury. J Immunol. 2006;176(10):6313-6322.
121. Anselmo DM, Amersi FF, Shen XD, et al. FTY720 pretreatment reduces warm hepatic ischemia reperfusion injury through inhibition of T-lymphocyte infiltration. Am J Transplant. 2002;2(9):843-849.
122. Shen XD, Ke B, Zhai Y, et al. CD154-CD40 T-cell costimulation pathway is required in the mechanism of hepatic ischemia/reperfusion injury, and its blockade facilitates and depends on heme oxygenase-1 mediated cytoprotection. Transplantation. 2002;74(3):315-319.
123. Ke B, Shen XD, Gao F, et al. The CD154-CD40 T-cell co-stimulation pathway in liver ischemia and reperfusion inflammatory responses. Transplantation. 2005;79(9):1078-1083.
124. Shimamura K, Kawamura H, Nagura T, et al. Association of NKT cells and granulocytes with liver injury after reperfusion of the portal vein. Cell Immunol. 2005;234(1):31-38.
125. Khandoga A, Hanschen M, Kessler JS, Krombach F. CD4+ T cells contribute to postischemic liver injury in mice by interacting with sinusoidal endothelium and platelets. Hepatology. 2006;43(2):306-315.
126. Li W, Lu L, Wang Z, et al. Il-12 antagonism enhances apoptotic death of T cells within hepatic allografts from Flt3 ligand-treated donors and promotes graft acceptance. J Immunol. 2001;166(9):5619-5628.
127. Lappas CM, Day YJ, Marshall MA, Engelhard VH, Linden J. Adenosine A2A receptor activation reduces hepatic ischemia reperfusion injury by inhibiting CD1d-dependent NKT cell activation. J Exp Med. 2006;203(12):2639-2648.
128. Odashima M, Otaka M, Jin M, et al. A selective adenosine A2A receptor agonist, ATL-146e, prevents concanavalin A-induced acute liver injury in mice. Biochem Biophys Res Commun. 2006;347(4):949-954.
129. Hamada T, Tsuchihashi S, Avanesyan A, et al. Cyclooxygenase-2 deficiency enhances Th2 immune responses and impairs neutrophil recruitment in hepatic ischemia/reperfusion injury. J Immunol. 2008;180(3):1843-1853.
130. Pulitanò C, Sitia G, Aldrighetti L, et al. Reduced severity of liver ischemia/reperfusion injury following hepatic resection in humans is associated with enhanced intrahepatic expression of Th2 cytokines. Hepatol Res. 2006;36(1):20-26.
131. Moore C, Shen XD, Fondevila C, Gao F, Coito AJ. Blockade of fibronectin-alpha4beta1 adhesive interactions down-regulates cyclooxygenase-2 inducible nitric oxide synthase and prolongs recipient survival in a 24-hour model of cold hepatic ischemia-reperfusion injury. Transplant Proc. 2005;37(4):1682-1683.
132. Amersi F, Shen XD, Moore C, et al. Fibronectin-alpha 4 beta 1 integrin-mediated blockade protects genetically fat Zucker rat livers from ischemia/reperfusion injury. Am J Pathol. 2003;162(4):1229-1239.
133. Xue H, Guo H, Li YC, Hao ZM. Heme oxygenase-1 induction by hemin protects liver cells from ischemia/reperfusion injury in cirrhotic rats. World J Gastroenterol. 2007;13(40):5384-5390.
134. Tsuchihashi S, Zhai Y, Fondevila C, Busuttil RW, Kupiec-Weglinski JW. HO-1 upregulation suppresses type 1 IFN pathway in hepatic ischemia/reperfusion injury. Transplant Proc. 2005;37(4):1677-1678.
135. Kato H, Amersi F, Buelow R, et al. Heme oxygenase-1 over-expression protects rat livers from ischemia/reperfusion injury with extended cold preservation. Am J Transplant. 2001;1(2):121-128.
136. Ke QH, Zheng SS, Liang TB, Xie HY, Xia WL. [Effects of hypertonic saline on expression of heme oxygenase enzyme-1 in hepatic ischemia/reperfusion injury rats] Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2006;18(1):5-8. Chinese.
137. Lai IR, Chang KJ, Tsai HW, Chen CF. Pharmacological pre-conditioning with simvastatin protects liver from ischemia-reperfusion injury by heme oxygenase-1 induction. Transplantation. 2008;85(5):732-738.
138. Coito AJ, Buelow R, Shen XD, et al. Heme oxygenase-1 gene transfer inhibits inducible nitric oxide synthase expression and protects genetically fat Zucker rat livers from ischemia-reperfusion injury. Transplantation. 2002;74(1):96-102.
139. Ke B, Buelow R, Shen XD, et al. Heme oxygenase 1 gene transfer prevents CD95/Fas ligand-mediated apoptosis and improves liver allograft survival via carbon monoxide signaling pathway. Hum Gene Ther. 2002;13(10):1189-1199.
140. Tsuchihashi S, Zhai Y, Bo Q, Busuttil RW, Kupiec-Weglinski JW. Heme oxygenase-1 mediated cytoprotection against liver ischemia and reperfusion injury: inhibition of type-1 interferon signaling. Transplantation. 2007;83(12):1628-1634.
141. Nakahira K, Takahashi T, Shimizu H, et al. Protective role of heme oxygenase-1 induction in carbon tetrachloride-induced hepatotoxicity. Biochem Pharmacol. 2003;66(6):1091-1105.
142. Wen T, Guan L, Zhang YL, Zhao JY. Dynamic changes of heme oxygenase-1 and carbon monoxide production in acute liver injury induced by carbon tetrachloride in rats. Toxicology. 2006;228(1):51-57.
143. Lee CH, Park SW, Kim YS, et al. Protective mechanism of glycyrrhizin on acute liver injury induced by carbon tetrachloride in mice. Biol Pharm Bull. 2007;30(10):1898-1904.
144. Eipel C, Eisold M, Schuett H, Vollmar B. Inhibition of heme oxygenase-1 protects against tissue injury in carbon tetrachloride exposed livers. J Surg Res. 2007;139(1):113-120.
145. Wang XH, Wang K, Zhang F, et al. Heme oxygenase-1 alleviates ischemia/reperfusion injury in aged liver. World J Gastroenterol. 2005;11(5):690-694.
146. Fondevila C, Shen XD, Tsuchiyashi S, et al. Biliverdin therapy protects rat livers from ischemia and reperfusion injury. Hepatology. 2004;40(6):1333-1341.
147. Kato Y, Shimazu M, Kondo M, et al. Bilirubin rinse: A simple protectant against the rat liver graft injury mimicking heme oxygenase-1 preconditioning. Hepatology. 2003;38(2):364-373.
148. Kaizu T, Ikeda A, Nakao A, et al. Protection of transplant-induced hepatic ischemia/reperfusion injury with carbon monoxide via MEK/ERK1/2 pathway downregulation. Am J Physiol Gastrointest Liver Physiol. 2008;294(1):G236-G244.
149. Kaizu T, Nakao A, Tsung A, et al. Carbon monoxide inhalation ameliorates cold ischemia/reperfusion injury after rat liver transplantation. Surgery. 2005;138(2):229-235.
150. Wen T, Zhao JY, Mei S, Guan L, Zhang YL. [Protective effect of heme oxygenase-1 and its reaction product, carbon monoxide on acute liver injury induced by carbon tetrachloride in rats] Beijing Da Xue Xue Bao. 2006;38(6):618-622. Chinese.
151. Amersi F, Shen XD, Anselmo D, et al. Ex vivo exposure to carbon monoxide prevents hepatic ischemia/reperfusion injury through p38 MAP kinase pathway. Hepatology. 2002;35(4):815-823.
152. Yamagami K, Enders G, Schauer RJ, et al. Heat-shock preconditioning protects fatty livers in genetically obese Zucker rats from microvascular perfusion failure after ischemia reperfusion. Transpl Int. 2003;16(8):456-463.
153. Yamagami K, Yamamoto Y, Toyokuni S, Hata K, Yamaoka Y. Heat shock preconditioning reduces the formation of 8-hydroxy-2'-deoxyguanosine and 4-hydroxy-2-nonenal modified proteins in ischemia-reperfused liver of rats. Free Radic Res. 2002;36(2):169-176.
154. Matsuo K, Togo S, Sekido H, et al. Pharmacologic preconditioning effects: prostaglandin E1 induces heat-shock proteins immediately after ischemia/reperfusion of the mouse liver. J Gastrointest Surg. 2005;9(6):758-768.

155. Shen SQ, Zhang Y, Xiang JJ, Xiong CL. Protective effect of curcumin against liver warm ischemia/reperfusion injury in rat model is associated with regulation of heat shock protein and antioxidant enzymes. World J Gastroenterol. 2007;13(13):1953-1961.
156. Bedirli A, Sakrak O, Muhtaroglu S, et al. Ergothioneine pretreatment protects the liver from ischemia-reperfusion injury caused by increasing hepatic heat shock protein 70. J Surg Res. 2004;122(1):96-102.
157. Shen SQ, Zhang Y, Xiong CL. The protective effects of 17beta-estradiol on hepatic ischemia-reperfusion injury in rat model, associated with regulation of heat-shock protein expression. J Surg Res. 2007;140(1):67-76.
158. Ikeyama S, Kusumoto K, Miyake H, Rokutan K, Tashiro S. A non-toxic heat shock protein 70 inducer, geranylgeranylacetone, suppresses apoptosis of cultured rat hepatocytes caused by hydrogen peroxide and ethanol. J Hepatol. 2001;35(1):53-61.
159. Shi Q, Dong Z, Wei H. The involvement of heat shock proteins in murine liver regeneration. Cell Mol Immunol. 2007;4(1):53-57.
160. Noh J, Behrends M, Choi S, et al. Glutamine does not protect against hepatic warm ischemia/reperfusion injury in rats. J Gastrointest Surg. 2006;10(2):234-239.
161. Sakai T, Takaya S, Fukuda A, Harada O, Kobayashi M. Evaluation of warm ischemia-reperfusion injury using heat shock protein in the rat liver. Transpl Int. 2003;16(2):88-99.
162. Chen H, Yu YY, Zhang MJ, et al. Protective effect of doxorubicin induced heat shock protein 72 on cold preservation injury of rat livers. World J Gastroenterol. 2004;10(9):1375-1378.
163. Cheng Y, Liu YF, Liang J. Protective effect of zinc: a potent heat shock protein inducer in cold preservation of rat liver. Hepatobiliary Pancreat Dis Int. 2002;1(2):258-261.
164. Boeri D, Dondero F, Storace D, Maiello M, Pasqualini M, Pellicci R. Heat-shock protein 70 favours human liver recovery from ischaemia-reperfusion. Eur J Clin Invest. 2003;33(6):500-504.
165. Uchinami H, Yamamoto Y, Kume M, et al. Effect of heat shock preconditioning on NF-kappaB/I-kappaB pathway during I/R injury of the rat liver. Am J Physiol Gastrointest Liver Physiol. 2002;282(6):G962-G971.
166. Chen H, Peng CH, Deng XX, et al. [The protective effect of heat shock protein 72 by Doxorubicin in cold ischemia-reperfusion injury of the rat liver] Zhonghua Wai Ke Za Zhi. 2006;44(5):310-313. Chinese.
167. Doi Y, Hamazaki K, Yabuki M, Tanaka N, Utsumi K. Effect of HSP70 induced by warm ischemia to the liver on liver function after partial hepatectomy. Hepatogastroenterology. 2001;48(38):533-540.
168. Kuboki S, Schuster R, Blanchard J, Pritts TA, Wong HR, Lentsch AB. Role of heat shock protein 70 in hepatic ischemia-reperfusion injury in mice. Am J Physiol Gastrointest Liver Physiol. 2007;292(4):G1141-G1149.
169. Galloway E, Shin T, Huber N, et al. Activation of hepatocytes by extracellular heat shock protein 72. Am J Physiol Cell Physiol. 2008;295(2):C514-C520.
170. Li F, Chong ZZ, Maiese K. Erythropoietin on a tightrope: balancing neuronal and vascular protection between intrinsic and extrinsic pathways. Neurosignals. 2004;13(6):265-289.
171. Maiese K, Chong ZZ, Li F, Shang YC. Erythropoietin: elucidating new cellular targets that broaden therapeutic strategies. Prog Neurobiol. 2008;85(2):194-213.
172. Yilmaz S, Ates E, Tokyol C, Pehlivan T, Erkasap S, Koken T. The protective effect of erythropoietin on ischaemia/reperfusion injury of liver. HPB (Oxford). 2004;6(3):169-173.
173. Hochhauser E, Pappo O, Ribakovsky E, et al. Recombinant human erythropoietin attenuates hepatic injury induced by ischemia/reperfusion in an isolated mouse liver model. Apoptosis. 2008;13(1):77-86.
174. Sepodes B, Maio R, Pinto R, et al. Recombinant human erythropoietin protects the liver from hepatic ischemia-reperfusion injury in the rat. Transpl Int. 2006;19(11):919-926.
175. Schmeding M, Neumann UP, Boas-Knoop S, Spinelli A, Neuhaus P. Erythropoietin reduces ischemia-reperfusion injury in the rat liver. Eur Surg Res. 2007;39(3):189-197.
176. Solaroglu A, Dede FS, Okutan E, Bayrak A, Haberal A, Kilinc K. A single dose of erythropoietin attenuates lipid peroxidation in experimental liver ischemia-reperfusion injury in the rat fetus. J Matern Fetal Neonatal Med. 2004;16(4):231-234.
177. Schmeding M, Boas-Knoop S, Lippert S, et al. Erythropoietin promotes hepatic regeneration after extended liver resection in rats. J Gastroenterol Hepatol. 2008;23(7 Pt 1):1125-1131.
178. Yazihan N, Ataoğlu H, Yener B, Aydin C. Erythropoietin attenuates hydrogen peroxide-induced damage of hepatocytes. Turk J Gastroenterol. 2007;18(4):239-244.
179. Ates E, Yilmaz S, Ihtiyar E, Yasar B, Karahuseyinoglu E. Pre-conditioning-like amelioration of erythropoietin against laparoscopy-induced oxidative injury. Surg Endosc. 2006;20(5):815-819.
180. Calvey CR, Toledo-Pereyra LH. Selectin inhibitors and their proposed role in ischemia and reperfusion. J Invest Surg. 2007;20(2):71-85.
181. Kubes P, Payne D, Woodman RC. Molecular mechanisms of leukocyte recruitment in postischemic liver microcirculation. Am J Physiol Gastrointest Liver Physiol. 2002;283(1):G139-G147.
182. Khandoga A, Biberthaler P, Enders G, et al. P-selectin mediates platelet-endothelial cell interactions and reperfusion injury in the mouse liver in vivo. Shock. 2002;18(6):529-535.
183. Tsuchihashi S, Fondevila C, Shaw GD, et al. Molecular characterization of rat leukocyte P-selectin glycoprotein ligand-1 and effect of its blockade: protection from ischemia-reperfusion injury in liver transplantation. J Immunol. 2006;176(1):616-624.
184. Amersi F, Farmer DG, Shaw GD, et al. P-selectin glycoprotein ligand-1 (rPSGL-Ig)-mediated blockade of CD62 selectin molecules protects rat steatotic liver grafts from ischemia/reperfusion injury. Am J Transplant. 2002;2(7):600-608.
185. Amersi F, Dulkanchainun T, Nelson SK, et al. A novel iron chelator in combination with a P-selectin antagonist prevents ischemia/reperfusion injury in a rat liver model. Transplantation. 2001;71(1):112-118.
186. Zhou T, Sun GZ, Zhang MJ, et al. Role of adhesion molecules and dendritic cells in rat hepatic/renal ischemia-reperfusion injury and anti-adhesive intervention with anti-P-selectin lectin-EGF domain monoclonal antibody. World J Gastroenterol. 2005;11(7):1005-1010.
187. Rivera-Chavez FA, Toledo-Pereyra LH, Martinez-Mier G, et al. L-selectin blockade and liver function in rats after uncontrolled hemorrhagic shock. J Invest Surg. 2001;14(1):7-12.
188. Taut FJ, Schmidt H, Zapletal CM, et al. N-acetylcysteine induces shedding of selectins from liver and intestine during orthotopic liver transplantation. Clin Exp Immunol. 2001;124(2):337-341.
189. Young CS, Palma JM, Mosher BD, et al. Hepatic ischemia/reperfusion injury in P-selectin and intercellular adhesion molecule-1 double-mutant mice. Am Surg. 2001;67(8):737-744.
190. López-Neblina F, Toledo-Pereyra LH. Anti-ischemic effect of selectin blocker through modulation of tumor necrosis factor-alpha and interleukin-10. J Surg Res. 2007;138(2):275-283.
191. Toledo-Pereyra LH, Lopez-Neblina F, Reuben JS, Toledo AH, Ward PA. Selectin inhibition modulates Akt/MAPK signaling and chemokine expression after liver ischemia-reperfusion. J Invest Surg. 2004;17(6):303-313.
192. Toledo-Pereyra LH, Lopez-Neblina F, Lentsch AB, Anaya-Prado R, Romano SJ, Ward PA. Selectin inhibition modulates NF-kappa B and AP-1 signaling after liver ischemia/reperfusion. J Invest Surg. 2006;19(5):313-322.
193. Shinoda M, Shimazu M, Matsuda S, et al. c-Jun N-terminal kinase activation during warm hepatic ischemia/reperfusion injuries in a rat model. Wound Repair Regen. 2002;10(5):314-319.
194. Mollen KP, McCloskey CA, Tanaka H, et al. Hypoxia activates c-Jun N-terminal kinase via Rac1-dependent reactive oxygen species production in hepatocytes. Shock. 2007;28(3):270-277.
195. Uehara T, Xi Peng X, Bennett B, et al. c-Jun N-terminal kinase mediates hepatic injury after rat liver transplantation. Transplantation. 2004;78(3):324-332.
196. Uehara T, Bennett B, Sakata ST, et al. JNK mediates hepatic ischemia reperfusion injury. J Hepatol. 2005;42(6):850-859.
197. Crenesse D, Laurens M, Heurteaux C, et al. Rat liver ischemia-reperfusion-induced apoptosis and necrosis are decreased by FK506 pretreatment. Eur J Pharmacol. 2003;473(2-3):177-184.

198. Lee KH, Kim SE, Lee YS. SP600125, a selective JNK inhibitor, aggravates hepatic ischemia-reperfusion injury. Exp Mol Med. 2006;38(4):408-416.
199. Zhao Y, Man K, Lo CM, et al. Attenuation of small-for-size liver graft injury by FTY720: significance of cell-survival Akt signaling pathway. Am J Transplant. 2004;4(9):1399-1407.
200. Man K, Ng KT, Lee TK, et al. FTY720 attenuates hepatic ischemia-reperfusion injury in normal and cirrhotic livers. Am J Transplant. 2005;5(1):40-49.
201. Kobayashi M, Takeyoshi I, Yoshinari D, Matsumoto K, Morishita Y. P38 mitogen-activated protein kinase inhibition attenuates ischemia-reperfusion injury of the rat liver. Surgery. 2002;131(3):344-349.
202. Kobayashi K, Oshima K, Muraoka M, et al. Effect of atrial natriuretic peptide on ischemia-reperfusion injury in a porcine total hepatic vascular exclusion model. World J Gastroenterol. 2007;13(25):3487-3492.
203. Shiotani S, Shimada M, Suehiro T, et al. Involvement of Rho-kinase in cold ischemia-reperfusion injury after liver transplantation in rats. Transplantation. 2004;78(3):375-382.
204. Ikeda F, Terajima H, Shimahara Y, Kondo T, Yamaoka Y. Reduction of hepatic ischemia/reperfusion-induced injury by a specific ROCK/Rho kinase inhibitor Y-27632. J Surg Res. 2003;109(2):155-160.
205. Kawaguchi A, Ohmori M, Fujimura A. Partial protective effect of Y-27632, a Rho kinase inhibitor, against hepatic ischemia-reperfusion injury in rats. Eur J Pharmacol. 2004;493(1-3):167-171.
206. Takeda K, Jin MB, Fujita M, et al. A novel inhibitor of Rho-associated protein kinase, Y-27632, ameliorates hepatic ischemia and reperfusion injury in rats. Surgery. 2003;133(2):197-206.
207. Mizunuma K, Ohdan H, Tashiro H, Fudaba Y, Ito H, Asahara T. Prevention of ischemia-reperfusion-induced hepatic microcirculatory disruption by inhibiting stellate cell contraction using rock inhibitor. Transplantation. 2003;75(5):579-586.
208. Ikeda H, Kume Y, Tejima K, et al. Rho-kinase inhibitor prevents hepatocyte damage in acute liver injury induced by carbon tetrachloride in rats. Am J Physiol Gastrointest Liver Physiol. 2007;293(4):G911-G917.
209. Shiotani S, Shimada M, Taketomi A, et al. Rho-kinase as a novel gene therapeutic target in treatment of cold ischemia/reperfusion-induced acute lethal liver injury: effect on hepatocellular NADPH oxidase system. Gene Ther. 2007;14(19): 1425-1433.
210. Lee MH, Murphy G. Matrix metalloproteinases at a glance. J Cell Sci. 2004;117(Pt 18):4015-4016.
211. Fowell AJ, Benyon RC. Can matrix metalloproteinases be targeted in hepatic ischemia/reperfusion injury? Hepatology. 2008;47(1): 14-16.
212. Defamie V, Laurens M, Patrono D, et al. Matrix metalloproteinase inhibition protects rat livers from prolonged cold ischemia-warm reperfusion injury. Hepatology. 2008;47(1):177-185.
213. Cursio R, Mari B, Louis K, et al. Rat liver injury after normothermic ischemia is prevented by a phosphinic matrix metalloproteinase inhibitor. FASEB J. 2002;16(1):93-95.
214. Shirahane K, Yamaguchi K, Koga K, Watanabe M, Kuroki S, Tanaka M. Hepatic ischemia/reperfusion injury is prevented by a novel matrix metalloproteinase inhibitor, ONO-4817. Surgery. 2006;139(5):653-664.
215. Chen CF, Leu FJ, Chen HI, Wang D. Oxygen radicals and matrix metalloproteinases mediate reperfusion liver injury. Transplant Proc. 2005;37(10):4547-4549.
216. Kuyvenhoven JP, Molenaar IQ, Verspaget HW, et al. Plasma MMP-2 and MMP-9 and their inhibitors TIMP-1 and TIMP-2 during human orthotopic liver transplantation. The effect of aprotinin and the relation to ischemia/reperfusion injury. Thromb Haemost. 2004;91(3):506-513.
217. Kuyvenhoven JP, Ringers J, Verspaget HW, Lamers CB, van Hoek B. Serum matrix metalloproteinase MMP-2 and MMP-9 in the late phase of ischemia and reperfusion injury in human orthotopic liver transplantation. Transplant Proc. 2003;35(8):2967-2969.
218. Moore C, Shen XD, Gao F, Busuttil RW, Coito AJ. Fibronectin-alpha4beta1 integrin interactions regulate metalloproteinase-9 expression in steatotic liver ischemia and reperfusion injury. Am J Pathol. 2007;170(2):567-577.
219. Hamada T, Fondevila C, Busuttil RW, Coito AJ. Metalloproteinase-9 deficiency protects against hepatic ischemia/reperfusion injury. Hepatology. 2008;47(1):186-198.
220. Khandoga A, Kessler JS, Hanschen M, et al. Matrix metalloproteinase-9 promotes neutrophil and T cell recruitment and migration in the postischemic liver. J Leukoc Biol. 2006;79(6):1295-1305.
221. Frangogiannis NG. Chemokines in ischemia and reperfusion. Thromb Haemost. 2007;97(5):738-747.
222. Harada H, Wakabayashi G, Takayanagi A, et al. Transfer of the interleukin-1 receptor antagonist gene into rat liver abrogates hepatic ischemia-reperfusion injury. Transplantation. 2002;74(10):1434-1441.
223. Zhai Y, Qiao B, Gao F, et al. Type I, but not type II, interferon is critical in liver injury induced after ischemia and reperfusion. Hepatology. 2008;47(1):199-206.
224. Motoki A, Adachi N, Liu K, et al. Suppression of ischaemia-induced cytokine release by dimaprit and amelioration of liver injury in rats. Basic Clin Pharmacol Toxicol. 2008;102(4):394-398.
225. Kato A, Graul-Layman A, Edwards MJ, Lentsch AB. Promotion of hepatic ischemia/reperfusion injury by IL-12 is independent of STAT4. Transplantation. 2002;73(7):1142-1145.
226. Takiguchi M, Totsuka E, Umehara M, et al. Attenuation of microcirculatory disturbance after liver ischemia by newly synthesized inflammatory cytokine suppressor, FR167653. Hepatogastroenterology. 2003;50(51):789-793.
227. Ben-Ari Z, Hochhauser E, Burstein I, et al. Role of anti-tumor necrosis factor-alpha in ischemia/reperfusion injury in isolated rat liver in a blood-free environment. Transplantation. 2002;73(12):1875-1880.
228. Takeuchi D, Yoshidome H, Kato A, et al. Interleukin 18 causes hepatic ischemia/reperfusion injury by suppressing anti-inflammatory cytokine expression in mice. Hepatology. 2004;39(3):699-710.
229. Conzelmann LO, Lehnert M, Kremer M, Zhong Z, Wheeler MD, Lemasters JJ. Graft tumor necrosis factor receptor-1 protects after mouse liver transplantation whereas host tumor necrosis factor receptor-1 promotes injury. Transplantation. 2006;82(9):1214-1220.
230. Guidi L, Tricerri A, Costanzo M, et al. Interleukin-6 release in the hepatic blood outflow during normothermic liver ischaemia in humans. Dig Liver Dis. 2003;35(6):409-415.
231. Ke B, Shen XD, Tsuchihashi S, et al. Viral interleukin-10 gene transfer prevents liver ischemia-reperfusion injury: Toll-like receptor-4 and heme oxygenase-1 signaling in innate and adaptive immunity. Hum Gene Ther. 2007;18(4):355-366.
232. Ke QH, Zheng SS, Liang TB, Xie HY, Xia WL. Pretreatment of hypertonic saline can increase endogenous interleukin 10 release to attenuate hepatic ischemia reperfusion injury. Dig Dis Sci. 2006;51(12):2257-2263.
233. Oreopoulos GD, Wu H, Szaszi K, et al. Hypertonic preconditioning prevents hepatocellular injury following ischemia/reperfusion in mice: a role for interleukin 10. Hepatology. 2004;40(1):211-220.
234. Kawakami T, Takahashi T, Shimizu H, et al. Highly liver-specific heme oxygenase-1 induction by interleukin-11 prevents carbon tetrachloride-induced hepatotoxicity. Int J Mol Med. 2006;18(4):537-546.
235. Kato A, Okaya T, Lentsch AB. Endogenous IL-13 protects hepatocytes and vascular endothelial cells during ischemia/reperfusion injury. Hepatology. 2003;37(2):304-312.