Review Article

Protective Role of mTOR in Liver Ischemia/Reperfusion Injury: Involvement of Inflammation and Autophagy

Tao Zhang, Jianrong Guo, Jian Gu, Ke Chen, Huili Li, and Jiliang Wang

Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

Correspondence should be addressed to Huili Li; huili_li@hust.edu.cn and Jiliang Wang; jiliang_wang@hust.edu.cn

Received 29 May 2019; Revised 24 August 2019; Accepted 14 October 2019; Published 13 November 2019

Academic Editor: Paola Rizzo

Copyright © 2019 Tao Zhang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Liver ischemia/reperfusion (IR) injury is a common phenomenon after liver resection and transplantation, which often results in liver graft dysfunction such as delayed graft function and primary nonfunction. The mammalian target of rapamycin (mTOR) is an evolutionarily highly conserved serine/threonine protein kinase, which coordinates cell growth and metabolism through sensing environmental inputs under physiological or pathological conditions, involved in the pathophysiological process of IR injury. In this review, we mainly present current evidence of the beneficial role of mTOR in modulating inflammation and autophagy under liver IR to provide some evidence for the potential therapies for liver IR injury.

1. Introduction

Liver resection and transplantation are the most effective approaches for liver cancer and other end-stage liver diseases. However, liver ischemia/reperfusion (IR) injury is a common complication after liver surgery, which is characterized by aggravated hepatocellular damage in the ischemic liver after the restoration of blood flow [1]. Additionally, abdominal trauma, myocardial ischemia, stroke, and hemorrhagic shock can also cause insufficient liver blood flow, resulting in liver IR injury after reperfusion. Liver IR injury can be divided into warm IR injury and cold IR injury, based on different ischemia conditions. The warm IR injury develops during liver surgery and various forms of shock and trauma, while the cold IR injury occurs during liver transplantation [2]. The severity of the injury ranges from moderate serum aminotransferase level increase to postoperative liver failure after liver resection or to delayed graft function and even primary nonfunction after liver transplantation [3]. Thus, it is of vital importance to investigate the underlying mechanisms and search for possible interventions to protect the liver from IR injury.

Various factors are involved in the pathophysiological process of liver IR injury, including active oxygen species (ROS) overproduction, excessive inflammatory response (redundant inflammatory cytokine release and activation of complement system), the overactivation of autophagy and endoplasmic reticulum stress (ERS), and mitochondrial dysfunction [2]. Among all these factors, inflammation and autophagy are two critical ones. Mammalian target of rapamycin (mTOR) is a critical regulator of cell growth and metabolism that senses and integrates various signals under physiological and pathological conditions, playing critical roles in regulating liver IR injury [4–9].

In this review, we will focus on the role of mTOR signaling in regulating inflammation and autophagy processes in liver IR injury, highlighting the protective role of mTOR signaling and providing some evidence for the potential therapies for liver IR injury.

2. mTOR Signaling Pathway

The mammalian target of rapamycin (mTOR) is an evolutionarily highly conserved serine/threonine protein kinase that plays a vital role in regulating mRNA translation, metabolism, and protein turnover [10]. And its dysfunction relates to autoimmune diseases, cancer, obesity, and senescence [11]. mTOR combines with several proteins
to constitute two distinct complexes, named mTOR complexes 1 (mTORC1) and 2 (mTORC2). mTORC1 is composed of five components: mTOR, regulatory protein associated with mTOR (Raptor), mammalian lethal with Sec13 protein 8 (mLST8 or G6L), proline-rich Akt substrate of 40 kDa (PRAS40), and DEP domain containing mTOR interacting protein (DEPTOR). mTORC2 is composed of mTOR, rapamycin insensitive companion of mTOR (Rictor), mLST8, DEPTOR, and the regulatory subunits mSin1 and Protor1/2 [10]. mTORC1 integrates stimuli from intracellular and extracellular cues, such as growth factors, energy status, amino acids, stress, and oxygen, and is sensitive to rapamycin. mTORC1 plays a crucial role in controlling protein, lipid, nucleotide, and glucose metabolism, autophagy, energy metabolism, lysosome biogenesis, cell survival, and cytoskeletal organization [12]. mTORC2 is insensitive to nutrients and acute rapamycin treatment but sensitive to growth factors [12], which regulate cell cytoskeletal remodeling, cell migration, glucose metabolism, ion transport, and cell survival [10]. Moreover, mTORC2 can phosphorylate and activate Akt (on S473), a major effector of the insulin/PI3K pathway, which is essential for the activation of mTORC1 [10]. Besides, mTORC2 can also be phosphorylated and activated by Akt in the subunit of mSin1 (on T86) [13]. Since mTORC1 is the better characterized and well-studied mTOR complex and exerts major regulatory function on various fundamental cell processes, we will mainly focus on mTORC1 in this review.

mTORC1 integrates upstream signaling molecules such as growth factors (insulin), epidermal growth factor (EGF), amino acids, energy, stress, and mitogens via multiple signaling pathways [14]. There exist four major upstream signaling pathways of mTORC1, including the insulin/phosphatidylinositol-3 kinase/protein kinase B (insulin/PI3K/Akt) signaling pathway, EGF/Ras/Raf/mitogen activated protein kinase (EGF/Ras/Raf/Mek/Erk) signaling pathway, Wnt/glycogen synthase kinase-3β (Wnt/GSK-3β) signaling pathway, and adenosine monophosphate-activated protein kinase (AMPK) signaling pathway [12, 15]. All of these four axes are converged at least partially on tuberous sclerosis complex (TSC), which is composed of TSC1, TSC2, and TBC1D7 and functions as a GTPase activating protein (GAP) of the Ras homolog enriched in brain (Rheb) GTPase. The GDP-bound form of Rheb directly binds and activates mTORC1 activity. As a GAP of Rheb, TSC converts GTP-Rheb into its inactive GDP-bound form to inhibit the activity of mTORC1 [10] (Figure 1).

3. The mTOR Signaling and Liver IR

3.1. Inhibition of mTOR Signaling in Liver IR. The inhibition of mTOR signaling during liver IR has been shown in many studies [5, 6, 9]. Hypoxia/ischemia, oxidative stress, and DNA damage are commonly involved in liver IR injury [16], which suppress mTOR through various molecular pathways.

Under conditions of hypoxia/ischemia, liver AMPK is activated in a very short window of time (about 2 min) to respond to the increased intracellular AMP/ATP and/or ADP/ATP ratio [17, 18]. Activated AMPK suppresses mTORC1 by phosphorylating TSC (on S1345) to amplify the inhibitory activity of TSC to mTORC1 [19]. Besides, AMPK directly phosphorylates Raptor (on S792), a component of mTORC1, leading to the allosteric inhibition of mTORC1 [19]. In addition, hypoxia/ischemia inhibits mTORC1 also through mediating regulated in DNA damage and development 1 (REDD1) in hepatocytes [20]. In response to hypoxia/ischemia, the expression of REDD1 is transcriptionally upregulated [21]. REDD1 converges on TSC and promotes TSC-mediated suppression of mTORC1 through mediating 14-3-3 protein shuttling from TSC to REDD1 [15].

Oxidative stress, known as redox balance dysregulation and overproduction of ROS, also exerts inhibitory effects on mTORC1 [22–28]. Antioxidants such as N-acetylcysteine [29] and hydrogen sulfide [8, 30] can effectively restore the activity of mTORC1, which is repressed by oxidative stress in organ IR injury, including the liver. The mechanisms behind may be as follows: ROS can activate TSC to suppress the activation of mTORC1 [31]. Besides, ROS also inhibits mTORC1 through activating cytoplasmic ataxia telangiec-tasia mutated (ATM) [22, 25]. Activated ATM further activates TSC [22] or phosphorylates HIF1α, leading to the activation of REDD1 [32], resulting in the inhibition of mTORC1. Additionally, H2O2-induced ROS burst can induce the activation of activator protein-1 (AP-1), which transcriptionally regulates the activation of REDD1 in hepatocytes [33], leading to the suppression of mTORC1. Moreover, ROS can inhibit mTORC1 through activating AMPK as well [24, 34].

Finally, the DNA damage will lead to the activation of p53, which causes the activation of TSC2, phosphatase and tensin homolog deleted on chromosome 10 (PTEN), and β1 subunits of the AMPK (AMPKβ1), resulting in the suppression of mTORC1 [35] (Figure 1).

3.2. The Beneficial Effects of mTOR Signaling in Liver IR Injury. The beneficial effects of mTOR in IR have been observed in the heart [36–43], brain [44–47], intestine [48, 49], and kidney [50]. Similarly, the protective function of mTOR signaling in liver IR injury has been revealed in some studies (Table 1). Bortezomib [4], melatonin [5], geniposide [7], NaHS [8], and agonim-miR–494 [9] administration attenuated liver IR injury through activating mTOR signaling. Additionally, genetic overexpression of liver mTOR directly significantly reduces liver inflammation and apoptosis induced by IR [6].

In this review, we focused on the impact of mTOR signaling on inflammatory response and autophagy to discuss the beneficial effect of mTOR signaling on liver IR injury.

4. mTOR Attenuates Inflammation Response in Liver IR Injury

An excessive inflammatory response is recognized as a key mechanism of liver IR injury. Inflammatory networks, including inflammatory cells and humoral factors, play a vital role in liver IR injury [51]. Kupffer cells (KCs), neutrophils, CD4+ T lymphocytes, and natural killer T (NKT) cells are the main cellular participants. Complement factors, cytokines, and
chemokines are the main humoral factors. Additionally, sinusoidal endothelial cells (SECs) and hepatocytes are also important participants and play critical roles in the inflammatory response during the liver IR process, leading to hepatocellular damage [52].

The mTOR signaling is appreciated to be a potent activator of the immune response, as its role in regulating cellular metabolism which is closely related to the proliferation and activation of immune cells, including neutrophils, mast cells, macrophages, dendritic cells (DCs), T lymphocytes, and B cells.

**Figure 1:** The mTOR signaling pathway is involved in liver IR injury and plays crucial roles in autophagy. Growth factors such as insulin activates mTORC1 through the PI3K/Akt/mTORC1 pathway. However, the activation of the AMPK signaling pathway will lead to the inhibition of mTORC1 through activating TSC. Hypoxia/ischemia, oxidative stress, and DNA damage are mechanisms commonly involved in liver IR injury. The decrease of ATP induced by hypoxia/ischemia activates AMPK, which inhibits mTORC1 through activating TSC or suppressing mTOR directly. Additionally, hypoxia/ischemia also activates REDD1, which promotes the TSC-mediated suppression of mTOR. Oxidative stress induces the activation of ATM, which inhibits mTORC1 through activating TSC directly or through phosphorylating HIF1α, resulting in induction of REDD1, causing the activation of TSC. Besides, oxidative stress promotes the activation of AP-1, which transcriptionally upregulates the expression of REDD1. Finally, DNA damage inhibits mTOR through inducing PTEN, AMPKβ1, and TSC, which are targeted by p53. mTOR signaling plays a crucial and complex role in autophagy. In the initial phase of autophagy, mTORC1 inhibits ULK complex (ULK1/Atg13/Atg101/FIP200) via directly phosphorylating ULK1 and ATG13. Besides, mTORC1 can also inhibit ULK complex through phosphorylating and suppressing AMBRA, which enhances the activity and stability of ULK1. Additionally, mTORC1 represses the initial of autophagy also through inhibiting VPS34 complex (VPS34/VPS15/Beclin1/ATG14/NRBF2) by directly phosphorylating ATG14 and NRBF2. In the elongation/closure phase, mTORC1 suppresses autophagic and lysosomal biogenesis through phosphorylating TFEB and TFE3 to modulate their nuclear-cytoplasmic shuttling. Moreover, mTORC1 can also augment autophagy through phosphorylating DAP1, which acts as a buffering mechanism that counterbalances the autophagic flux and prevents its overactivation. Additionally, mTORC2 also participated in the induction of autophagy through an unclear mechanism.
However, an increasing body of evidence has emerged indicating that mTOR plays a pivotal anti-inflammatory role in liver IR injury. Myeloid mTOR activation through PTEN deficiency leads to the suppression of liver immune activation and protected livers from IR injury [55]. Additionally, mTOR-deficient mice showed greater expression levels of inflammation-related genes such as MCP-1, TNF-α, and IL-6 than wild-type (WT) mice after liver IR via negatively modulating NF-κB [6]. Besides, the opposite effect was seen in TSC1-deficient (mTOR-activated) mice, which showed a weaker inflammation response to liver IR injury than WT mice [6]. However, the mechanism of...
mTOR signaling in regulating the inflammatory response in liver IR injury largely remains unclear. In this section, we will discuss the regulatory role of mTOR signaling on inflammatory cells and humoral factors in liver IR injury (Figure 2).

4.1. Kupffer Cells (KCs). KCs, the liver-resident macrophages, play a key role in initiating and propagating inflammatory response of liver IR injury. In the early stage of reperfusion (within 2h), KCs are activated by damage-associated
molecular patterns (DAMPs), such as high-mobility group box 1 protein (HMGB1) and DNA fragments, through activating Toll-like receptor 4 (TLR4) [56]. On activation, KCs release ROS and proinflammatory molecules, including IL-1β and TNF-α. ROS induces oxidative damages to proteins, enzymes, nucleic acids, cytoskeleton, and lipid, leading to mitochondrial dysfunction and lipid peroxidation, contributing to injury of hepatocytes and SECs, resulting in both apoptotic and necrotic cell death [57]. ROS can also activate NF-κB, which upregulates the expression of proinflammatory cytokines, including TNF-α [58]. IL-1β activates NF-κB and macrophage inflammatory protein-2 (MIP-2), leading to the aggregation and adhesion of neutrophils [59]. TNF-α recruits and activates neutrophils and CD4+ T lymphocytes to the site of injury [60].

Numbers of studies have revealed the impact of mTOR signaling on KCs (or macrophages). The inhibition of mTORC1 increases inflammation and promotes the recruitment of inflammatory macrophages by enhancing NF-κB activity [61]. The Akt/mTOR signaling pathway can convert proinflammatory M1 macrophage into the anti-inflammatory M2 type through regulating the expression and phosphorylation of Acly [62]. Acly is a key enzyme in Ac-CoA synthesis, which increases the production of Ac-CoA in M2 macrophages and leads to the activation of M2 macrophages, resulting in the suppression of inflammation [62]. Besides, the Akt/mTOR signaling pathway can also integrate metabolic signals to support the activation of M2 macrophage [62]. However, researchers also found that increased activity of mTORC1 by ablating TSC1 promoted M1 macrophage polarization and suppressed M2 macrophage polarization [63]. The controversial results may be due to the fact that macrophage polarization is also regulated by environmental cues. And the different environmental and metabolic cues sensed by mTOR signaling influence macrophage polarization in some complex and unknown manners [64]. In the context of liver IR injury, astaxanthin activated the Akt/mTOR/HIF-1α signaling pathway in KCs, reducing the production of ROS and the expression of inflammatory cytokines, attenuating liver IR injury [65]. Similarly, activation of mTORC1 induced by PTEN deficiency promotes the M2 polarization of macrophages and increases the production of IL-10, decreasing the release of TNF-α, IL-6, and IL-12 when responding to TLR stimulation in liver IR injury [66]. Additionally, the deficiency of Rictor, a core component of mTORC2, increases the infiltration of macrophage/neutrophil and the release of cytokine/chemokine during liver IR injury [67], indicating an important role of mTORC2 on suppressing KCs.

4.2. Neutrophils. The activation of neutrophils is the major cause of injury in the late phase of liver IR (between 6 and 24 h after reperfusion) [68]. As described above, during the first 2 h of reperfusion, KCs activate and release ROS and proinflammatory cytokines, including TNF-α, which upregulates intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin on the surface of SECs and hepatocytes, leading to the accumulation of neutrophils in the sinusoidal space and causing microcirculatory disturbances [69]. Additionally, neutrophils migrate toward the site of injury through extravasation and chemotaxis [70]. The accumulation of neutrophils in the site of injury leads to hepatocellular damages through degranulation with release of a large amount of proteases and ROS [71]. Additionally, neutrophils propagate the inflammatory response by recruiting other members of the immune system [72].

The mTOR signaling plays critical roles in the proliferation and activation of neutrophils [53, 54]. Rapamycin promotes the infiltration of neutrophils through inducing the expression of ICAM-1 via the activation of NF-κB in endothelial cells, indicating that mTORC1 can inhibit the migration of neutrophils [73]. Besides, in the liver [67] and kidney [74] IR injury, mTORC2 suppresses the infiltration of neutrophils and attenuates organ IR injury. However, the role and mechanism of mTOR signaling (especially mTORC1) on regulating neutrophils in IR injury remain unclear, and further studies are needed to investigate.

4.3. CD4+ T Lymphocytes. CD4+ T lymphocytes are important cellular participants of inflammation response in liver IR injury, which plays a critical role in promoting liver IR injury [75–77]. As described above, the activation of KCs can activate CD4+ T lymphocytes through releasing TNF-α. Activated CD4+ T lymphocytes release granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-β, and INF-γ, which in turn amplify the activation of KCs and promote the recruitment of neutrophils into the liver sinusoids [78, 79]. What is more, CD4+ T lymphocytes can also recruit neutrophils through producing IL-17 [80].

mTOR signaling is crucial for the differentiation of CD4+ T lymphocytes [81]. However, the role and mechanism of mTOR signaling on regulating CD4+ T lymphocytes in liver IR injury remain unclear; further investigations are needed to reveal.

4.4. Natural Killer T (NKT) Cells. Natural killer T (NKT) cells are a kind of markedly enriched nonconventional T cells in the liver, accounting for up to 30% of the intrahepatic lymphocytes [82]. NKT cells are divided into two subtypes: Type I (invariant, iNKT) and Type II; iNKT accounts for the majority [83]. The high abundance of iNKT cells in the liver and their rapid response (within hours) to activation suggest that they might play a role in liver IR injury [83, 84]. iNKT cells are recruited to the postschismic liver and are activated through interacting with CD1d antigen-presenting molecules, which express on hepatocytes and antigen-presenting cells (APC) within the liver. Activated iNKT cells damage the liver directly through secreting perforin and FasL and indirectly through activating neutrophils by the production of IFN-γ [85, 86]. Reducing the recruitment and cytokine production of iNKT cells ameliorates liver IR injury [87, 88]. Contrary to iNKT cells, Type II NKT cells have an anti-inflammatory effect [89].

Several studies have demonstrated the importance of mTOR in iNKT cells. mTOR signaling plays a critical role for both early and late stages of iNKT cell development [90]. However, the role and mechanism of mTOR signaling
5.1. Definition of Autophagy. Autophagy is an evolutionarily highly conserved self-degradative process that targets intracellular components to lysosomes for degradation and recycling to maintaining cellular homeostasis [98]. There are four recognized types of autophagy: macroautophagy, microautophagy, chaperone-mediated autophagy (CMA), and noncanonical autophagy [99]. Here, we will focus on macroautophagy, which will be henceforth referred to as autophagy.

In nutrient-rich conditions, autophagy holds at a low level to maintain intracellular homeostasis through the removal of long-lived and malformed proteins and damaged organelles, called basal autophagy [100]. The activity of cellular autophagy can be markedly upregulated by starvation, hypoxia, energy depletion, ERS, infection, and other stimuli, which are called induced autophagy [101]. Upon induction, small double-membrane vesicles, called autophagosomes, sequester proteins, damaged organelles, and exogenous pathogens. And then, the outer membrane of autophagosomes fuses with lysosomes to form autolysosomes, in which the cargos and inner membrane of autophagosomes were degraded into biological active macromolecules (amino acids, nucleotide, free fatty acids, etc.) and be recycled for the synthesis of protein and ATP [102]. Furthermore, autophagy also plays a pivotal role in cellular homeostasis by regulating the turnover of mitochondria [103], ER [104], peroxisomes [105], and lipid [106] through selective forms. Nevertheless, excessive autophagy, leading to excessive degradation of essential proteins and organelles, can also induce a programmed cell death, called Type II programmed cell death [107]. Additionally, there also exist crosstalks between autophagy and other cell death mechanisms, including apoptosis and necrosis [108].

5.2. Autophagy and Liver IR Injury. An increasing body of evidence has emerged indicating that autophagy plays pivotal roles in IR injury of the heart [109], liver [3], brain [110], kidney [111], and lung [112], whereas its role remains controversial in these organs. Recent studies indicated that autophagy acts as a double-edged sword in either a beneficial or a detrimental way in ischemia and reperfusion phases, respectively. Autophagy acts as a compensatory mechanism to counterbalance ATP deprivation in the stage of ischemia, while sustained and excessive activation of autophagy during reperfusion phase results in cell death [113]. It was proven by multiple types of research in heart [114], liver [115], and brain [116] IR injuries. Additionally, a recent study found in the model of hypoxia/reoxygenation of adipose-derived mesenchymal stem cells (ADMSC) that the autophagy of ADMSC activated in the initial hypoxia period and markedly enhanced in the phase of reoxygenation. Interestingly, in the hypoxia phase, apelin upregulated protective autophagy through activating the AMPK/mTOR/ULK1 pathway. In the reoxygenation period, apelin suppressed excessive autophagy through Akt/Bcl2/Becn1 signaling [117]. Similarly, berberine exerts protective effects in IR injury both through activating autophagy [118] and suppressing excessive autophagy [119]. The dual modulative effects of apelin and berberine keep autophagy activity at a moderate level to be protective for cell survival.

Accumulative evidence has shown that autophagy was hepatoprotective in liver IR injury [120–124]. However, some studies suggested that autophagy was deleterious in liver IR injury [5, 115, 125, 126]. The different results may be attributed to the various magnitudes of autophagy, owing to the different types of IR mode (cold/warm or partial/global IR) and the different liver conditions (lean/fatty), which lead to the different levels of autophagy activation. The controversial results may also owe to the “side effects” (except for regulating autophagy) of interventions adopted in the researches (Table 2).

5.3. mTOR Signaling and Autophagy. Autophagy can be regulated by the Bcl-2 signaling pathway, mTOR signaling pathway, MAPK signaling pathway, and p53 signaling pathway...
### Table 2: The relationship between autophagy and liver IR injury.

| Study          | Effect of autophagy | Animal model | Liver type | IR mode (ischemia/reperfusion time) | Autophagy change in IR | Interventions (effect on autophagy)                                                                 | “Side effects” of intervention                                                                 |
|----------------|---------------------|--------------|------------|-------------------------------------|------------------------|------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Lee et al. [121] | Protective          | BALB/c       | Lean       | Warm 75% (45 min/2, 3, 6, 12, and 24 h) | Increase              | Everolimus I (1 mg/kg each time, i.p.) 24 h before and immediately after reperfusion (+)          | Reduces inflammation and apoptosis [121]. Reduces HO-1 expression and increases iNOS level [161]. |
| Liu et al. [123] | Protective          | SD           | Lean       | Warm 75% (1 h/1 h, 6 h)              | Increase              | Baicalein (100 mg/kg, i.p.), 1 h prior to ischemia (+)                                             | Activates HO-1 [123], PTEN/Akt/NO pathway [162], Inhibits NF-κB [163] and MAPK pathway [164].   |
| Khader et al. [120] | Protective         | C57BL/6      | Lean       | Warm 70% (1 h/12 h)                  | Increase              | SRT1720 (20 mg/kg, i.v.) before reperfusion (+)                                                   | Stimulates the mitochondrial biogenesis. Reduces oxidative stress and inflammation [165].      |
| Yang et al. [124] | Protective          | C57BL/6      | Lean/fatty | Warm 75% (1 h/0.5, 1.5, 3, 6, 12, and 24 h) | Increase              | Tri-iodothyronine (0.002 mg, i.p.) precondition (+)                                              | Reduces oxidative stress, apoptosis, and inflammation. Activates MEK/ERK/mTORC1 pathway [124]. |
| Zhao et al. [166] | Protective          | C57BL/6      | Lean/fatty | Warm 75% (1 h/20 min)                | Increase              | Calpain inhibitor III (10 mg/kg, i.p.) 6 h prior to ischemia (+)                                 | Inhibits the degradation of structural proteins. Suppresses apoptosis. Alters Ca²⁺ handling [167]. |
| Li et al. [168]  | Detrimental         | C57BL/6      | Lean       | Warm 75% (1.5 h/2, 6, 12, and 24 h)  | Increase              | miR-17 agomir or antagonim (10 nM) 24 h prior to ischemia (+)                                    | Inhibits PTEN [169], STAT3 [168], and death receptor 6 (DR6) [170]. Inhibits oxidative stress. Improves the endothelial function. Restores mitochondrial function. Suppresses TLR and JNK pathways [94]. Activates RISK, SAFE, ERK1/2, PKB, PKC, JAK/STAT3, Sirt1/Sirt3, AMPKα, and Notch1/Mfn2 pathways [122]. |
| Kang et al. [5]  | Detrimental         | C57BL/6      | Lean       | Warm 75% (1 h/1, 5, and 24 h)        | Increase              | Melatonin (10 mg/kg, i.p.) 15 min prior to ischemia and again immediately before reperfusion (-) | Wortmannin (100 nM) or LY294002 (10 μM) was added to the UW solution in the in situ perfusion and during storage, respectively (-) | Inhibits PI3K/Akt pathway [115]. |
| Gotoh et al. [115] | Detrimental         | Wistar       | Lean       | Cold 100% (24 h/15 min)              | Increase              | Ethyl pyruvate (20 mg/kg, 40 mg/kg, and 80 mg/kg, i.v.) 1 h prior to ischemia (-)               | Inhibits HMGB1/TLR/NF-κB pathway [171], Suppresses oxidative stress [172] and apoptosis [126]. |
| Shen et al. [126] | Detrimental         | BALB/c       | Lean       | Warm 75% (45 min/4, 8, and 16 h)     | Increase              | Ex4 (20 μg/kg i.v.) 2 h prior to ischemia and immediately after surgery (-)                     | Activates Nrf2 [173], Akt/eNOS [174], and HMGB1 [175] pathways. |
| Study          | Effect of autophagy | Animal model | Liver type | IR mode (ischemia/reperfusion time) | Autophagy change in IR | Interventions (effect on autophagy)                                                                 | “Side effects” of intervention                                                                 |
|---------------|---------------------|--------------|------------|-------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Yun et al. [176] | Protective          | C57BL/6 Lean | Lean       | Warm 75% (1 h/1, 4, and 24 h)       | Decrease             | Hemin (30 mg/kg) 16 h and 3 h prior to ischemia; carbon monoxide-releasing molecule-2 (20 mg/kg, i.p.) immediately before reperfusion (+) | Activates HO-1 [176], nuclear factor-erythroid 2-related factor 2 (Nrf2) [177], Suppresses NF-κB p65 nuclear translocation [177] and calpain-2 [176]. |
| Kim et al. [178] | Protective          | C57BL/6 Lean | Lean       | Cold 100% (45 min/2 and 4 h)        | Decrease             | Carbamazepine (25 mg/kg, i.p.), overnight before IR (+) Melatonin and trimetazidine were added to the UW solution during graft storage for 24 h (+) | Inhibits MPT Ca^{2+} overload. Suppresses calpain-2 [178].                                     |
| Zaouali et al. [139] | Protective       | Zucker Fatty | Fatty      | Cold 100% (24 h/2 h)                | Decrease             | Same as above.                                                                                                                  |                                                                                               |
| Minor et al. [179] | Protective         | Wistar Fatty | Fatty      | Cold 100% (20 h/1.5 h and 2 h)      | Decrease             | Hypothermic reconditioning during the last 90 minutes of preservation (+)                                                      | Inhibits oxidative stress [179]. Enhances mitochondrial function [180].                         |

i.p.: intraperitoneal injection; i.v.: intravenous injection.
Among them, autophagy is mainly negatively regulated by the mTOR signaling pathway. Under physiology conditions, growth factors such as insulin or EGF activate mTORC1 through insulin/PI3-K/Akt/mTORC1 and EGF/Ras/Raf/Mek/Erk/mTORC1 axis, respectively. Activated mTOR signaling exerts a potent inhibitory effect on multiple phases of autophagy. In the initiation phase, mTORC1 suppresses autophagy by inhibiting ULK complex (ULK1/Atg13/ATG101/FIP200), a kinase complex indispensable to initiate autophagy via directly phosphorylating ULK1 (on S317) and ATG13. Besides, mTORC1 can also inhibit ULK complex through phosphorylating and suppressing Beclin 1-regulated autophagy protein 1 (AMBRA), which enhances the activity and stability of ULK1. Additionally, mTORC1 represses the initial of autophagy also through inhibiting another crucial complex for autophagy induction, vacuolar protein sorting 34 (VPS34) complex (VPS34/VPS15/Beclin1/ATG14/NRBF2), by directly phosphorylating ATG14 and nuclear receptor binding factor 2 (NRBF2) (on S133 and S120). In the elongation/closure phase, mTORC1 suppresses autophagic and lysosomal biogenesis through phosphorylating TFE3 (on S211) and TFE3 (on S321) to modulate their nuclear-cytoplasmic shuttling. Moreover, mTORC1 can also augment autophagy through phosphorylating death-associated protein 1 (DAP1), which acts as a buffering mechanism that counterbalances the autophagic flux and prevents its overactivation. Additionally, researchers found that the activation of mTORC2 also participated in the induction of autophagy.

As shown above, in conditions of hypoxia/ischemia, oxidative stress and DNA damage induced by liver IR, AMPK, REDD1, and ATM will be activated and lead to the suppression of mTOR signaling, resulting in the activation/overactivation of autophagy. Since the indispensable role of mTOR signaling on autophagy, numerous researches focused on mTOR signaling for regulating autophagy to protect against liver IR injury.
liver IR injury. Researches have shown that melatonin [5] and microRNA-101 [135] attenuated liver IR injury by suppressing autophagy through activating mTOR signaling. However, researches have also shown that activation of autophagy through mTOR inhibitor rapamycin [136–138] and everolimus [121] has been shown to protect against liver IR injury. In addition, a recent study showed that inhibition of mTORC2 by Rictor deficiency aggravated liver IR injury through suppressing autophagy [67]. The paradox result may be attributed to the double-edged effect of autophagy in liver IR injury that the moderate level of autophagy mitigated liver IR injury in ischemia, while the excessive level of autophagy aggravated liver IR injury in reperfusion. This explains the finding that in moderate and advanced steatotic liver that autophagy was impaired, melatonin combined with trimetazidine elevated liver autophagy, rather than inhibited, and improved liver IR injury [139].

These findings indicated an intricate function of autophagy in liver IR injury and a complexity effect of the mTOR pathway in regulating autophagy. We believe that moderate regulation of autophagy through modulating the PI3K/Akt/mTORC1 pathway or mTORC1/mTORC2 balancing may serve as a potential strategy for attenuating liver IR injury.

6. Conclusions

Liver IR injury is a clinical phenomenon in various settings including liver resection and transplantation, which is a major cause of morbidity and mortality in liver surgeries and limits the use of grafts available for transplantation.

Liver IR injury is typified by the excessive inflammatory response, which involves a complex interaction network between the inflammatory cells and humoral factors, leading to liver dysfunction and cell injury. Although mTOR signaling is a potent proinflammatory regulator on the growth and differentiation of multiple inflammatory cells, in the context of liver IR injury, it seems to play a significant role in anti-inflammation through regulating KCs and neutrophils. However, the mechanism of mTOR signaling on anti-inflammation still remains unclear, especially on the regulation of CD4+ T lymphocytes, NKT cells, and complement systems in the context of liver IR injury.

Additionally, significant changes of autophagy in hepatocytes are observed in liver IR injury; enhancing autophagy under ischemia conditions can promote survival, whereas excessive and long-term augmentation of autophagy during reperfusion may promote cell death. mTOR signaling plays a complexity effect in regulating autophagy. Keeping autophagy at a moderate level during liver IR through modulating the PI3K/Akt/mTORC1 pathway or mTORC1/mTORC2 balancing may serve as a potential strategy for attenuating liver IR injury. A comprehensive study and an illuminating evaluation of the mTOR pathway are thus needed before clinical usage of the autophagy regulator in liver IR patients.

However, in contrast to the beneficial effect of mTOR mentioned above, some studies have shown that berberine precondition [140], isoflurane precondition [141], and rapamycin dealing [138, 142], which associated with inhibition of mTOR signaling, also showed protective effects on liver IR injury, indicating a detrimental role of mTOR signaling in liver IR injury (Table 1). The controversial results may be due to the “side effects” (except for regulating mTOR) of the interventions and the different levels of autophagy in the liver IR models adopted in these researches (Table 1). Besides, Li et al. utilized complementary genetic models with gain or loss of function of mTOR signaling in the liver and demonstrated the beneficial effect of mTOR in liver IR injury [6]. Thus, we hold the idea that mTOR signaling plays a protective role in liver IR injury.

In a word, the impact of mTOR signaling on the inflammatory response and autophagy provides an attractive therapeutic target for liver IR injury (Figure 3).

Conflicts of Interest

All authors have declared no competing interest exists.

Acknowledgments

This study was supported by the Natural Science Foundation of China (No. 81570568 to Jiliang Wang and No. 81602419 to Huili Li).

References

[1] W. G. van Riel, R. van Golen, M. J. Reiniers, M. Heger, and T. van Gulik, “How much ischemia can the liver tolerate during resection?,” Hepatobiliary Surgery and Nutrition, vol. 5, no. 1, pp. 58–71, 2016.
[2] J. Li, R. J. Li, G. Y. Lv, and H. Q. Liu, “The mechanisms and strategies to protect from hepatic ischemia-reperfusion injury,” European Review for Medical and Pharmacological Sciences, vol. 19, no. 11, pp. 2036–2047, 2015.
[3] R. Cursio, P. Colosetti, and J. Gugenheim, “Autophagy and liver ischemia-reperfusion injury,” BioMed Research International, vol. 2015, Article ID 417590, 16 pages, 2015.
[4] M. Bejaoui, M. A. Zaouali, E. Folch-Puy et al., “Bortezomib enhances fatty liver preservation in Institut George Lopez-1 solution through adenosine monophosphate activated protein kinase and Akt/mTOR pathways,” Journal of Pharmacy and Pharmacology, vol. 66, no. 1, pp. 62–72, 2014.
[5] J. W. Kang, H. I. Cho, and S. M. Lee, “Melatonin inhibits mTOR-dependent autophagy during liver ischemia/reperfusion,” Cellular Physiology and Biochemistry, vol. 33, no. 1, pp. 23–36, 2014.
[6] Z. Li, J. Zhang, M. Mulholland, and W. Zhang, “mTOR activation protects liver from ischemia/reperfusion-induced injury through NF-κB pathway,” The FASEB Journal, vol. 31, no. 7, pp. 3018–3026, 2017.
[7] Y. P. Rong, H. T. Huang, J. S. Liu, and L. Wei, “Protective effects of geniposide on hepatic ischemia/reperfusion injury,” Transplantation Proceedings, vol. 49, no. 6, pp. 1455–1460, 2017.
[8] S. Shimada, M. Fukai, K. Wakayama et al., “Hydrogen sulfide augments survival signals in warm ischemia and reperfusion of the mouse liver,” Surgery Today, vol. 45, no. 7, pp. 892–903, 2015.
Oxidative Medicine and Cellular Longevity

[9] Su, S., Luo, X., Liu et al., "miR-494up-regulates the PI3K/Akt pathway via targeting PTEN and attenuates hepatic ischemia/reperfusion injury in a rat model," *Bioscience Reports*, vol. 37, no. 5, p. BSR20170798, 2017.

[10] Saxton and D. M. Sabatini, "mTOR signaling in growth, metabolism, and disease," *Cell*, vol. 168, no. 6, pp. 960–976, 2017.

[11] A. Perl, "mTOR activation is a biomarker and a central pathway to autoimmune disorders, cancer, obesity, and aging," *Annals of the New York Academy of Sciences*, vol. 1346, no. 1, pp. 33–44, 2015.

[12] D. S. Murashige, S. J. Humphrey, and D. E. James, "A positive feedback loop between Akt and mTORC2 via SIN1 phosphorylation," *Cell Reports*, vol. 12, no. 6, pp. 937–943, 2015.

[13] L. Chen, B. Xu, L. Liu et al., "Hydrogen peroxide inhibits mTORC1 and autophagy in response to ROS," *Molecular and Cellular Biology*, vol. 36, pp. 79–90, 2014.

[14] J. Gracia-Sancho, A. Casillas-Ramirez, and C. Peralta, "Molecular pathways in protecting the liver from ischemia/reperfusion injury: a 2015 update," *Clinical Science*, vol. 129, no. 4, pp. 345–362, 2015.

[15] K. Huang and D. C. Finkar, "Growing knowledge of the mTOR signaling network," *Seminars in Cell & Developmental Biology*, vol. 36, pp. 79–90, 2014.

[16] G. Yang, D. S. Murashige, S. J. Humphrey, and D. E. James, "A positive feedback loop between Akt and mTORC2 via SIN1 phosphorylation," *Cell Reports*, vol. 12, no. 6, pp. 937–943, 2015.

[17] D. G. Hardie, B. E. Schaffer, and A. Brunet, "AMPK: an energy-sensing pathway with multiple inputs and outputs," *Trends in Cell Biology*, vol. 26, no. 3, pp. 190–201, 2016.

[18] S. Majd, J. H. T. Power, T. K. Chataway, and H. J. M. Grantham, "A comparison of LKB1/AMPK/mTOR metabolic axis response to global ischemia in brain, heart, liver and kidney in a rat model of cardiac arrest," *BMC Cell Biology*, vol. 19, no. 1, p. 7, 2018.

[19] M. Gwinn, D. B. Shackelford, D. F. Egan et al., "AMPK phosphorylation of raptor mediates a metabolic checkpoint," *Molecular Cell*, vol. 30, no. 2, pp. 214–226, 2008.

[20] C. Wolf, S. Vega-Rubin-de-Celis, X. J. Xie, D. H. Castrillon, W. Kabbani, and J. Brugarolas, "Cell-type-dependent regulation of mTORC1 by REDD1 and the tumor suppressors TSC1/TSC2 and LKB1 in response to hypoxia," *Molecular and Cellular Biology*, vol. 31, no. 9, pp. 1870–1884, 2011.

[21] T. Shoshani, A. Faerman, I. Mett et al., "Identification of a novel hypoxia-inducible factor 1-responsive gene, RTP801, involved in apoptosis," *Molecular and Cellular Biology*, vol. 22, no. 7, pp. 2283–2293, 2002.

[22] A. Alexander, S. L. Cai, J. Kim et al., "ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS," *Proceedings of the National Academy of Sciences*, vol. 107, no. 9, pp. 4153–4158, 2010.

[23] Y. Byun, S. K. Kim, Y. M. Kim, G. T. Chae, S. W. Jeong, and S. B. Lee, "Hydrogen peroxide induces autophagic cell death in C6 glioma cells via BNIP3-mediated suppression of the mTOR pathway," *Neuroscience Letters*, vol. 461, no. 2, pp. 131–135, 2009.

[24] L. Chen, B. Xu, L. Liu et al., "Hydrogen peroxide inhibits mTOR signaling by activation of AMPKα leading to apoptosis of neuronal cells," *Laboratory Investigation*, vol. 90, no. 5, pp. 762–773, 2010.

[25] Z. Guo, S. Kozlov, M. F. Lavin, M. D. Person, and T. T. Paull, "ATM activation by oxidative stress," *Science*, vol. 330, no. 6003, pp. 517–521, 2010.

[26] G. Seo, S. K. Kim, Y. J. Byun et al., "Hydrogen peroxide induces Beclin 1-independent autophagic cell death by suppressing the mTOR pathway via promoting the ubiquitination and degradation of Rheb in GSH-depleted RAW 264.7 cells," *Free Radical Research*, vol. 45, no. 4, pp. 389–399, 2011.

[27] L. Zhang, S. R. Kimball, L. S. Jefferson, and J. S. Shenberger, "Hydrogen peroxide impairs insulin-stimulated assembly of mTORC1," *Free Radical Biology and Medicine*, vol. 46, no. 11, pp. 1500–1509, 2009.

[28] Q. Zhou, C. Liu, W. Liu et al., "Rotenone induction of hydrogen peroxide inhibits mTOR-mediated S6K1 and 4E-BP1/elf4E pathways, leading to neuronal apoptosis," *Toxico logical Sciences*, vol. 143, no. 1, pp. 81–96, 2015.

[29] S. Wang, C. Wang, F. Yan et al., "N-Acetylcysteine attenuates diabetic myocardial ischemia reperfusion injury through inhibiting excessive autophagy," *Mediators of Inflammation*, vol. 2017, Article ID 9257291, 10 pages, 2017.

[30] L. Xie, S. Yu, K. Yang, C. Li, and Y. Liang, "Hydrogen sulfide inhibits autophagic neuronal cell death by reducing oxidative stress in spinal cord ischemia reperfusion injury," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 8640284, 15 pages, 2017.

[31] J. Zhang, J. Kim, A. Alexander et al., "A tuberous sclerosis complex signalling node at the pexosome regulates mTORC1 and autophagy in response to ROS," *Nature Cell Biology*, vol. 15, no. 10, pp. 1186–1196, 2013.

[32] C. Cam, J. B. Easton, A. High, and P. J. Houghton, "mTORC1 Signaling under Hypoxic Conditions Is Controlled by ATM-Dependent Phosphorylation of HIF-1α," *Molecular Cell*, vol. 40, no. 4, pp. 509–520, 2010.

[33] S. S. Cho, K. M. Kim, J. H. Yang et al., "Induction of REDD1 via AP-1 prevents oxidative stress-mediated injury in hepatocytes," *Free Radical Biology and Medicine*, vol. 124, pp. 221–231, 2018.

[34] B. M. Emerling, F. Weinberg, C. Snyder et al., "Hypoxic activation of mTORC1 is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio," *Free Radical Biology and Medicine*, vol. 46, no. 10, pp. 1386–1391, 2009.

[35] Z. Feng, W. Hu, E. de Stanchina et al., "The regulation of AMPK beta1, TSC2, and PTEN expression by p53: stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-akt-mTOR pathways," *Cancer Research*, vol. 67, no. 7, pp. 3043–3053, 2007.

[36] T. Aoyagi, J. K. Higa, H. Aoyagi, N. Yorichika, B. K. Shimada, and T. Matsui, "Cardiac mTORC1 rescues the detrimental effects of diet-induced obesity in the heart against ischemia-reperfusion," *American Journal of Physiology: Heart and Circulatory Physiology*, vol. 308, no. 12, pp. H1530–H1539, 2015.

[37] T. Aoyagi, Y. Kusakari, C. Y. Xiao et al., "Cardiac mTOR protects the heart against ischemia-reperfusion injury," *American Journal of Physiology: Heart and Circulatory Physiology*, vol. 303, no. 1, pp. H75–H85, 2012.

[38] G. Fan, J. Yu, P. F. Asare et al., "Danshensu alleviates cardiac ischemia/reperfusion injury by inhibiting autophagy and apoptosis via activation of mTOR signalling," *Journal of Cellular and Molecular Medicine*, vol. 20, no. 10, pp. 1908–1919, 2016.

[39] H. P. Glazer, R. M. Ospino, R. T. Clements, F. W. Sellke, and C. Bianchi, "Hypercholesterolemia is associated with..."
hyperactive cardiac mTORC1 and mTORC2 signaling,” *Cell Cycle*, vol. 8, no. 11, pp. 1738–1746, 2009.

[40] S. C. Land and A. R. Tee, “Hypoxia-inducible factor 1alpha is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif,” *Journal of Biological Chemistry*, vol. 282, no. 28, pp. 20534–20543, 2007.

[41] P. C. Schenkel, A. M. V. Tavares, R. O. Fernandes et al., “Time course of hydrogen peroxide–thioredoxin balance and its influence on the intracellular signalling in myocardial infarction,” *Experimental Physiology*, vol. 97, no. 6, pp. 741–749, 2012.

[42] M. Zhang, D. Sun, S. Li et al., “Lin28a protects against cardiac ischaemia/reperfusion injury in diabetic mice through the insulin-P13K-mTOR pathway,” *Journal of Cellular and Molecular Medicine*, vol. 19, no. 6, pp. 1174–1182, 2015.

[43] Y. Zhou, H. Fang, S. Lin et al., “Qiliqiangxin protects against cardiac ischemia-reperfusion injury via activation of the mTOR pathway,” *Cellular Physiology and Biochemistry*, vol. 37, no. 2, pp. 454–464, 2015.

[44] O. Z. Chi, S. J. Mellender, S. Barsoum, X. Liu, S. Damito, and H. R. Weiss, “Effects of rapamycin pretreatment on blood-brain barrier disruption in cerebral ischemia-reperfusion,” *Neuroscience Letters*, vol. 620, pp. 132–136, 2016.

[45] L. Fu, L. Huang, C. Cao, Q. Yin, and J. Liu, “Inhibition of AMP-activated protein kinase alleviates focal cerebral ischemia injury in mice: interference with mTOR and autophagy,” *Brain Res*, vol. 1650, pp. 103–111, 2016.

[46] L. Xie, F. Sun, J. Wang et al., “mTOR signaling inhibition modulates macrophage/microglia-mediated neutrophilinflammation and secondary injury via regulatory T cells after focal ischemia,” *The Journal of Immunology*, vol. 192, no. 12, pp. 6009–6019, 2014.

[47] X. Yang, C. Hei, P. Liu et al., “Inhibition of mTOR pathway by rapamycin reduces brain damage in rats subjected to transient forebrain ischemia,” *International Journal of Biological Sciences*, vol. 11, no. 12, pp. 1424–1435, 2015.

[48] K. Ban and R. A. Kozar, “Protective role of p70S6K in intestinal ischemia/reperfusion injury in mice,” *PLoS One*, vol. 7, no. 7, p. e41584, 2012.

[49] H. Zhang, Z. Cui, G. Luo et al., “Ghrelin attenuates intestinal ischemia/reperfusion injury in mice by activating the mTOR signaling pathway,” *International Journal of Molecular Medicine*, vol. 32, no. 4, pp. 851–859, 2013.

[50] D. Fantus, N. M. Rogers, F. Grahammer, T. B. Huber, and A. W. Thomson, “Roles of mTOR complexes in the kidney: implications for renal disease and transplantation,” *Nature Reviews Nephrology*, vol. 12, no. 10, pp. 587–609, 2016.

[51] H. Jaeschke, “Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning,” *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 284, no. 1, pp. G15–G26, 2003.

[52] M. Abu-Amara, S. Y. Yang, N. Tapuria, B. Fuller, B. Davidson, and A. Seifalian, “Liver ischemia/reperfusion injury: Processes in inflammatory networks—A review,” *Liver Transplantation*, vol. 16, no. 9, pp. 1016–1032, 2010.

[53] S. P. Cobbold, “The mTOR pathway and integrating immune regulation,” *Immunology*, vol. 140, no. 4, pp. 391–398, 2013.

[54] J. D. Powell, K. N. Pollizzi, E. B. Heikamp, and M. R. Horton, “Regulation of immune responses by mTOR,” *Annual Review of Immunology*, vol. 30, no. 1, pp. 39–68, 2012.

[55] S. Yue, J. Rao, J. Zhu et al., “Myeloid PTEN deficiency protects livers from ischemia reperfusion injury by facilitating M2 macrophage differentiation,” *The Journal of Immunology*, vol. 192, no. 11, pp. 5343–5353, 2014.

[56] Q. Yang, Y. Liu, Y. Shi, M. Zheng, J. He, and Z. Chen, “The role of intracellular high-mobility group box 1 in the early activation of Kupffer cells and the development of Con A-induced acute liver failure,” *Immunobiology*, vol. 218, no. 10, pp. 1284–1292, 2013.

[57] H. Jaeschke, “Reactive oxygen and ischemia/reperfusion injury of the liver,” *Chemico-Biological Interactions*, vol. 79, no. 2, pp. 115–136, 1991.

[58] S. Sanlioglu, C. M. Williams, L. Samavati et al., “Lipopolysaccharide Induces Rac1-dependent Reactive Oxygen Species Formation and Coordinates Tumor Necrosis Factor-a Secretion through IKK Regulation of NF-xb,” *Journal of Biological Chemistry*, vol. 276, no. 32, pp. 30188–30198, 2001.

[59] B. M. Welborn III, L. L. Molderaw, J. M. Seeger, R. M. Minter, and T. S. Huber, “Role of endogenous interleukin-10 in local and distant organ injury after visceral ischemia-reperfusion,” *Shock*, vol. 20, no. 1, pp. 35–40, 2003.

[60] M. Hanschen, S. Zahler, F. Krombach, and A. Khandoga, “Reciprocal activation between CD4+ T cells and Kupffer cells during hepatic ischemia-reperfusion,” *Transplantation*, vol. 86, no. 5, pp. 710–718, 2008.

[61] T. Yoshihara, I. Mett, A. K. Bhunia et al., “Rtp801, a suppressor of mTOR signaling, is an essential mediator of cigarette smoke-induced pulmonary injury and emphysema,” *Nature Medicine*, vol. 16, no. 7, pp. 767–773, 2010.

[62] A. J. Covarrubias, H. I. Aksoylar, J. Yu et al., “Akt-mTORC1 signaling regulates Acly to integrate metabolic input to control of macrophage activation,” *Elife*, vol. 5, 2016.

[63] L. Zhu, T. Yang, L. Li et al., “TSC1 controls macrophage polarization to prevent inflammatory disease,” *Nature Communications*, vol. 5, no. 1, 2014.

[64] T. Weichhart, M. Hengstschlager, and M. Linke, “Regulation of innate immune cell function by mTOR,” *Nature Reviews Immunology*, vol. 15, no. 10, pp. 599–614, 2015.

[65] S. Li, T. Takahara, M. Fujino et al., “Astaxanthin prevents ischemia-reperfusion injury of the steatotic liver in mice,” *PLoS One*, vol. 12, no. 11, p. e0187810, 2017.

[66] N. Kamo, B. Ke, R. W. Busuttil, and J. W. Kupiec-Weglinski, “PTEN-mediated akt/β-Catenin/texol signaling regulates innate immune responses in mouse liver ischemia/reperfusion injury,” *Hepatology*, vol. 57, no. 1, pp. 289–298, 2013.

[67] D. Xu, J. Zhu, S. Jeong et al., “Rictor deficiency aggravates hepatic ischemia/reperfusion injury in mice by suppressing autophagy and regulating MAPK signaling,” *Cellular Physiology and Biochemistry*, vol. 45, no. 6, pp. 2199–2212, 2018.

[68] M. Elias-Miro, M. B. Jimenez-Castro, J. Rodes, and C. Peralta, “Current knowledge on oxidative stress in hepatic ischemia/reperfusion,” *Free Radical Research*, vol. 47, no. 8, pp. 555–568, 2013.

[69] B. Vollmar, J. Glasz, R. Leiderer, S. Post, and M. D. Menger, “Hepatic microcirculatory perfusion failure is a determinant of liver dysfunction in warm ischemia-reperfusion,” *The American Journal of Pathology*, vol. 145, no. 6, pp. 1421–1431, 1994.

[70] T. H. C. de Oliveira, P. E. Marques, P. Proost, and M. M. M. Teixeira, “Neutrophils: a cornerstone of liver ischemia and
reperfusion injury,” *Laboratory Investigation*, vol. 98, no. 1, article BFlabinvest201790, pp. 51–62, 2018.

[71] H. Jaeschke, “Mechanisms of liver injury. II. Mechanisms of neutrophil-induced liver cell injury during hepatic ischemia-reperfusion and other acute inflammatory conditions,” *American Journal of Pathology: Gastrointestinal and Liver Physiology*, vol. 290, no. 6, pp. G1083–G1088, 2006.

[72] K. M. Quesnelle, P. V. Bystrom, and L. H. Toledo-Pereyra, “Molecular responses to ischemia and reperfusion in the liver,” *Archives of Toxicology*, vol. 89, no. 5, pp. 651–657, 2015.

[73] M. Minhajuddin, F. Fazal, K. M. Bijli, M. R. Amin, and M. Howie, “Inhibition of Mammalian Target of Rapamycin Potentiates Thrombin-Induced Intercellular Adhesion Molecule-1 Expression by Accelerating and Stabilizing NF-kB Activation in Endothelial Cells,” *The Journal of Immunology*, vol. 174, no. 9, pp. 5823–5829, 2005.

[74] H. Dai, A. R. Watson, D. Fantus, L. Peng, A. W. Thomson, and N. M. Rogers, “Rictor deficiency in dendritic cells exacerbates acute kidney injury,” *Kidney International*, vol. 94, no. 5, pp. 951–963, 2018.

[75] S. Pommey, B. Lu, J. McRae et al., “Liver grafts from CD39-overexpressing rodents are protected from ischemia reperfusion injury due to reduced numbers of resident CD4+ T cells,” *Hepatology*, vol. 57, no. 4, pp. 1597–1606, 2013.

[76] J. Reifart, M. Rentsch, K. Mende et al., “Modulating CD4+ T cell migration in the postischemic liver: hepatic stellate cells as new therapeutic target?” *Transplantation*, vol. 99, no. 1, pp. 41–47, 2015.

[77] X. Shen, Y. Wang, F. Gao et al., “CD4 T cells promote tissue inflammation via CD40 signaling without de novo activation in a murine model of liver ischemia-reperfusion injury,” *Hepatology*, vol. 50, no. 5, pp. 1537–1546, 2009.

[78] C. C. Caldwell, J. Tschoep, and A. B. Lentsch, “Lymphocyte function during hepatic ischemia/reperfusion injury,” *Journal of Leukocyte Biology*, vol. 82, no. 3, pp. 457–464, 2007.

[79] A. Casillas-Ramirez, I. B. Mosbah, F. Ramalho, J. Roselló-Catafau, and C. Peralta, “Past and future approaches to ischemia-reperfusion lesion associated with liver transplantation,” *Life Sciences*, vol. 79, no. 20, pp. 1881–1894, 2006.

[80] C. C. Caldwell, T. Okaya, A. Martignoni, T. Husted, R. Schuster, and A. B. Lentsch, “Divergent functions of CD4+ T lymphocytes in acute liver inflammation and injury after ischemia-reperfusion,” *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 289, no. 5, pp. G969–G976, 2005.

[81] G. M. Delgoffe, K. N. Pollizzi, A. T. Waickman et al., “The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2,” *Nature Immunology*, vol. 12, no. 4, pp. 295–303, 2011.

[82] J. A. Richards, S. J. Wigmore, S. M. Anderton, and S. E. M. Howie, “NKT cells are important mediators of hepatic ischemia-reperfusion injury,” *Transplant Immunology*, vol. 45, pp. 15–21, 2017.

[83] M. Zimmerman, A. Martin, J. Yee, J. Schiller, and J. Hong, “Natural killer T cells in liver ischemia-reperfusion injury,” *Journal of Clinical Medicine*, vol. 6, no. 4, p. 41, 2017.

[84] C. M. Lappas, Y. J. Day, M. A. Marshall, V. H. Engelhard, and J. Linden, “Adenosine A2A receptor activation reduces hepatic ischemia reperfusion injury by inhibiting CD1d-dependent NKT cell activation,” *The Journal of Experimental Medicine*, vol. 203, no. 12, pp. 2639–2648, 2006.

[85] S. Kuboki, N. Sakai, J. Tschoep, M. J. Edwards, A. B. Lentsch, and C. C. Caldwell, “Distinct contributions of CD4+ T cell subsets in hepatic ischemia/reperfusion injury,” *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 296, no. 5, pp. G1054–G1059, 2009.

[86] L. Li, L. Huang, S. S. J. Sung et al., “NKT cell activation mediates neutrophil IFN-γ production and renal ischemia-reperfusion injury,” *The Journal of Immunology*, vol. 178, no. 9, pp. 5899–5911, 2007.

[87] K. Shimamura, H. Kawamura, T. Nagura et al., “Association of NKT cells and granulocytes with liver injury after reperfusion of the portal vein,” *Cellular Immunology*, vol. 234, no. 1, pp. 31–38, 2005.

[88] H. Zhu, Q. Zhang, and G. Chen, “CXCR6 deficiency ameliorates ischemia-reperfusion injury by reducing the recruitment and cytokine production of hepatic NKT cells in a mouse model of non-alcoholic fatty liver disease,” *International Immunopharmacology*, vol. 72, pp. 224–234, 2019.

[89] R. C. Halder, C. Aguilera, I. Maricic, and V. Kumar, “Type II NKT cell-mediated anergy induction in type I NKT cells prevents inflammatory liver disease,” *Journal of Clinical Investigation*, vol. 117, no. 8, pp. 2302–2312, 2007.

[90] W. Yang, B. Gorentla, X. P. Zhong, and J. Shin, “mTOR and its tight regulation for iNKT cell development and effector function,” *Molecular Immunology*, vol. 68, no. 2, pp. 536–545, 2015.

[91] E. E. Montalvo-Jave, T. Escalante-Tattersfield, J. A. Ortega-Salgado, E. Piña, and D. A. Geller, “Factors in the pathophysiology of the liver ischemia-reperfusion injury,” *Journal of Surgical Research*, vol. 147, no. 1, pp. 153–159, 2008.

[92] H. Jaeschke, A. Farhood, A. P. Bautista, Z. Spolarics, and J. J. Spitzer, “Complement activates Kupffer cells and neutrophils during reperfusion after hepatic ischemia,” *American Journal of Physiology*, vol. 264, no. 4, pp. G801–G809, 1993.

[93] T. M. Woodruff, T. V. Arumugam, I. A. Shiefs, R. C. Reid, D. P. Fairlie, and S. M. Taylor, “Protective effects of a potent C5a receptor antagonist on experimental acute limb ischemia-reperfusion injury in rats,” *Journal of Surgical Research*, vol. 116, no. 1, pp. 81–90, 2004.

[94] T. V. Arumugam, I. A. Shiefs, T. M. Woodruff, D. N. Granger, and S. M. Taylor, “The role of the complement system in ischemia-reperfusion injury,” *Shock*, vol. 21, no. 5, pp. 401–409, 2004.

[95] M. Kolev and C. Kemper, “Keeping it all going—complement meets metabolism,” *Frontiers in Immunology*, vol. 8, p. 1, 2017.

[96] K. Bish, W. Wegiel, J. Tampe et al., “Biliverdin modulates the expression of C5AR in response to endotoxin in part via mTOR signaling,” *Biological and Biophysical Research Communications*, vol. 449, no. 1, pp. 94–99, 2014.

[97] G. Chen, Z. Dong, H. Liu et al., “mTOR signaling regulates protective activity of transferred CD4+Foxp3+ T cells in repair of acute kidney injury,” *The Journal of Immunology*, vol. 197, no. 10, pp. 3917–3926, 2016.

[98] Z. Yang and D. J. Klionsky, “Eaten alive: a history of macroautophagy,” *Nature Cell Biology*, vol. 12, no. 9, pp. 814–822, 2010.
[99] N. Mizushima, T. Yoshimori, and Y. Ohsumi, “The role of Atg proteins in autophagosome formation,” *Annual Review of Cell and Developmental Biology*, vol. 27, no. 1, pp. 107–132, 2011.

[100] A. Kuma and N. Mizushima, “Physiological role of autophagy as an intracellular recycling system: with an emphasis on nutrient metabolism,” *Seminars in Cell & Developmental Biology*, vol. 21, no. 7, pp. 683–690, 2010.

[101] A. Kuma, M. Hatano, M. Matsui et al., “The role of autophagy during the early neonatal starvation period,” *Nature*, vol. 432, no. 7020, pp. 1032–1036, 2004.

[102] E. White, J. M. Mehnert, and C. S. Chan, “Autophagy, metabolism, and cancer,” *Clinical Cancer Research*, vol. 21, no. 22, pp. 5037–5046, 2015.

[103] I. Kim, S. Rodriguez-Enriquez, and J. J. Lemasters, “Selective degradation of mitochondria by mitophagy,” *Archives of Biochemistry and Biophysics*, vol. 462, no. 2, pp. 245–253, 2007.

[104] A. Khamineh, T. Heinrich, M. Mari et al., “Regulation of endoplasmic reticulum turnover by selective autophagy,” *Nature*, vol. 522, no. 7556, pp. 354–358, 2015.

[105] J. C. Farre, R. Manjithaya, R. D. Mathewson, and S. Subramani, “PpAtg30 tags peroxisomes for turnover by selective autophagy,” *Developmental Cell*, vol. 14, no. 3, pp. 365–376, 2008.

[106] R. Singh, S. Kaushik, Y. Wang et al., “Autophagy regulates lipid metabolism,” *Nature*, vol. 458, no. 7242, pp. 1131–1135, 2009.

[107] E. H. Bachrache, “Autophagic programmed cell death in *Drosophila*,” *Cell Death Differ*, vol. 10, no. 9, pp. 940–945, 2003.

[108] R. Khandia, M. Dadar, A. Munjal et al., “A comprehensive review of autophagy and its various roles in infectious, non-infectious, and lifestyle diseases: current knowledge and prospects for disease prevention, novel drug design, and therapy,” *Cells*, vol. 8, no. 7, p. 674, 2019.

[109] S. Ma, Y. Wang, Y. Chen, and F. Cao, “The role of the autophagy in myocardial ischemia/reperfusion injury,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1852, no. 2, pp. 271–276, 2015.

[110] Y. C. Wang, S. Zhang, T. Y. du, B. Wang, and X. Q. Sun, “Hyperbaric oxygen preconditioning reduces ischemia-reperfusion injury by stimulating autophagy in neurocyte,” *Brain Research*, vol. 1323, pp. 149–151, 2010.

[111] J. P. Decuyper, L. J. Culemans, P. Agostinis et al., “Autophagy and the kidney: implications for ischemia-reperfusion injury and therapy,” *American Journal of Kidney Diseases*, vol. 66, no. 4, pp. 699–709, 2015.

[112] S. W. Ryter and A. M. K. Choi, “Autophagy in the lung,” *Proceedings of the American Thoracic Society*, vol. 7, no. 1, pp. 13–21, 2010.

[113] L. J. Daniels, U. Varma, M. Annandale, E. Chan, K. M. Mellor, and L. M. D. Delbridge, “Myocardial energy stress, autophagy induction, and cardiomyocyte functional responses,” *Antioxidants & Redox Signaling*, vol. 31, no. 6, pp. 472–486, 2019.

[114] Y. Matsui, H. Takagi, X. Qu et al., “Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin 1 in mediating autophagy,” *Circulation Research*, vol. 100, no. 6, pp. 914–922, 2007.

[115] K. Gotoh, Z. Lu, M. Morita et al., “Participation of autophagy in the initiation of graft dysfunction after rat liver transplantation,” *Autophagy*, vol. 5, no. 3, pp. 351–360, 2009.

[116] W. Liu, G. Shang, S. Yang et al., “Electroacupuncture protects against ischemic stroke by reducing autophagosome formation and inhibiting autophagy through the mTORC1-ULK1 complex–Beclin1 pathway,” *International Journal of Molecular Medicine*, vol. 37, no. 2, pp. 309–318, 2016.

[117] D. Liang, D. Han, W. Fan et al., “Therapeutic efficacy of apelin on transplanted mesenchymal stem cells in hindlimb ischemic mice via regulation of autophagy,” *Scientific Reports*, vol. 6, no. 1, article 21914, 2016.

[118] Y. Lin, M. Sheng, Y. Weng et al., “Berberine protects against ischemia/reperfusion injury after orthotopic liver transplantation via activating Sirt1/FoxO3α induced autophagy,” *Biochimica and Biophysical Research Communications*, vol. 483, no. 2, pp. 885–891, 2017.

[119] Z. Huang, Z. Han, B. Ye et al., “Berberine alleviates cardiac ischemia/reperfusion injury by inhibiting excessive autophagy in cardiomyocytes,” *European Journal of Pharmacology*, vol. 762, pp. 1–10, 2015.

[120] A. Khader, W. L. Yang, A. Godwin et al., “Sirtuin 1 stimulation attenuates ischemic liver injury and enhances mitochondrial recovery and autophagy,” *Critical Care Medicine*, vol. 44, no. 8, pp. e651–e663, 2016.

[121] S. C. Lee, K. H. Kim, O. H. Kim, S. K. Lee, and S. J. Kim, “Activation of Autophagy by Everolimus Confers Hepatoprotection Against Ischemia–Reperfusion Injury,” *American Journal of Transplantation*, vol. 16, no. 7, pp. 2042–2054, 2016.

[122] A. Liu, H. Fang, W. Wei, O. Dirsch, and U. Dahmen, “Ischemic preconditioning protects against liver ischemia/reperfusion injury via heme oxygenase-1-mediated autophagy,” *Critical Care Medicine*, vol. 42, no. 12, pp. e762–e771, 2014.

[123] A. Liu, L. Huang, E. Guo et al., “Baicalin pretreatment reduces liver ischemia/reperfusion injury via induction of autophagy in rats,” *Scientific Reports*, vol. 6, no. 1, 2016.

[124] J. Yang, Y. Wang, M. Sui, F. Liu, Z. Fu, and Q. X. Wang, “Tri-iodothyronine preconditioning protects against liver ischemia reperfusion injury through the regulation of autophagy by the MEK/ERK/mTORC1 axis,” *Biochemical and Biophysical Research Communications*, vol. 467, no. 4, pp. 704–710, 2015.

[125] N. A. Gupta, V. L. Kolachala, R. Jiang et al., “Mitigation of autophagy ameliorates hepatocellular damage following ischemia-reperfusion injury in murine steatotic liver,” *American Journal of Physiology: Gastrointestinal and Liver Physiology*, vol. 307, no. 11, pp. G1088–G1099, 2014.

[126] M. Shen, J. Lu, W. Dai et al., “Activation of Autophagy by Everolimus Confers Hepatoprotection Against Ischemia–Reperfusion Injury,” *American Journal of Transplantation*, vol. 16, no. 7, pp. 2042–2054, 2016.

[127] A. L. Swampillai, P. Salomoni, and S. C. Short, “The role of autophagy in clinical practice,” *Annual Review of Biomedical Engineering*, vol. 16, no. 7, pp. 940–945, 2013.
R. Tan, H. Tian, B. Yang et al., “Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy,” *Molecular Biology of the Cell*, vol. 20, no. 7, pp. 1981–1991, 2009.

C. H. Jung, C. B. Jun, S. H. Ro et al., “ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery,” *Molecular Biology of the Cell*, vol. 20, no. 7, pp. 1992–2003, 2009.

D. Nazio, F. Strappazzon, M. Antonioli et al., “mTOR inhibits autophagy by controlling ULK1 ubiquitylation, self-association and function through AMBRA1 and TRAF6,” *Nature Cell Biology*, vol. 15, no. 4, pp. 406–416, 2013.

I. Koren, E. Reem, and A. Kimchi, “DAP1, a novel substrate of mTOR, negatively regulates autophagy,” *Current Biology*, vol. 20, no. 12, pp. 1093–1098, 2010.

N. Gurusamy, I. Lekli, S. Mukherjee et al., “Cardioprotection by resveratrol: a novel mechanism via autophagy involving the mTORC2 pathway,” *Cardiovascular Research*, vol. 86, no. 1, pp. 103–112, 2010.

H. Song, C. du, X. Wang, J. Zhang, and Z. Shen, “MicroRNA-101 inhibits autophagy to alleviate liver ischemia/reperfusion injury via regulating the mTOR signaling pathway,” *International Journal of Molecular Medicine*, vol. 43, no. 3, pp. 1331–1342, 2019.

R. Tan, H. Tian, B. Yang et al., “Autophagy and Akt in the protective effect of erythropoietin helix B surface peptide against hepatic ischaemia/reperfusion injury in mice,” *Scientific Reports*, vol. 8, no. 1, p. 14703, 2018.

D. Wang, Y. Ma, Z. Li et al., “The role of AKT1 and autophagy in the protective effect of hydrogen sulphide against hepatic ischemia/reperfusion injury in mice,” *Autophagy*, vol. 8, no. 6, pp. 954–962, 2012.

J. Zhu, T. Lu, S. Yue et al., “Rapamycin protection of livers from ischemia and reperfusion injury is dependent on both autophagy induction and mammalian target of rapamycin complex 2-Akt activation,” *Transplantation*, vol. 99, no. 1, pp. 48–55, 2015.

M. A. Zauouali, E. Boncompagni, R. J. Reiter et al., “AMPK involvement in endoplasmic reticulum stress and autophagy modulation after fatty liver graft preservation: a role for melanotin and trimetazidine cocktail,” *Journal of Pineal Research*, vol. 55, no. 1, pp. 65–78, 2013.

M. Sheng, Y. Zhou, W. Yu, Y. Weng, R. Xu, and H. du, “Protective effect of Berberine pretreatment in hepatic ischemia/reperfusion injury of rat,” *Transplantation Proceedings*, vol. 47, no. 2, pp. 275–282, 2015.

Z. Ruo, X. Pan, H. Zhang et al., “Isoflurane preconditioning alleviated murine liver ischemia and reperfusion injury by restoring AMPK/mTOR-mediated autophagy,” *Anesthesia and Analgesia*, vol. 125, no. 4, pp. 1355–1363, 2017.

J. Zhu, X. Hua, D. Li, J. Zhang, and Q. Xia, “Rapamycin attenuates mouse liver ischemia and reperfusion injury by inhibiting endoplasmic reticulum stress,” *Transplantation Proceedings*, vol. 47, no. 6, pp. 1646–1652, 2015.

V. Tiriveedhi, G. A. Upadhya, R. A. Busch et al., “Protective role of bortezomib in steatotic liver ischemia/reperfusion injury through abrogation of MMP activation and YKL-40 expression,” *Transplant Immunology*, vol. 30, no. 2-3, pp. 93–98, 2014.

F. T. Chen, C. M. Yang, and C. H. Yang, “The protective effects of the proteasome inhibitor bortezomib (velcade) on ischemia-reperfusion injury in the rat retina,” *PLoS One*, vol. 8, no. 5, p. e64262, 2013.

S. Ramachandran, J. M. Liaw, J. Jia et al., “Ischemia-reperfusion injury in rat steatotic liver is dependent on NFXB P65 activation,” *Transplant Immunology*, vol. 26, no. 4, pp. 201–206, 2012.

M. A. Zauouali, F. Bardag-Gorce, T. Carbonell et al., “Proteasome inhibitors protect the steatotic and non-steatotic liver graft against cold ischemia reperfusion injury,” *Experimental and Molecular Pathology*, vol. 94, no. 2, pp. 352–359, 2013.

J. Kim, H. Y. Kim, and S. M. Lee, “Protective effects of geniposide and genipin against hepatic ischemia/reperfusion injury in mice,” *Biomolecules and Therapeutics*, vol. 21, no. 2, pp. 132–137, 2013.

Y. Q. Jiang, G. L. Chang, Y. Wang, D. Y. Zhang, L. Cao, and J. Liu, “Geniposide prevents hypoxia/reoxygenation-induced apoptosis in H9c2 cells: improvement of mitochondrial dysfunction and activation of GLP-1R and the PI3K/AKT signaling pathway,” *Cellular Physiology and Biochemistry*, vol. 39, no. 1, pp. 407–421, 2016.

D. Wu, J. Wang, H. Li, M. Xue, A. Ji, and Y. Li, “Role of hydrogen sulfide in ischemia-reperfusion injury,” *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 186908, 16 pages, 2015.

G. Sun, Y. Zhou, H. Li et al., “Over-expression of microRNA-494 up-regulates hypoxia-inducible factor-1 alpha expression via PI3K/Akt pathway and protects against hypoxia-induced apoptosis,” *Journal of Biomedical Science*, vol. 20, no. 1, p. 100, 2013.

X. Wang, X. Zhang, X. P. Ren et al., “MicroRNA-494 targeting both proapoptotic and antiapoptotic proteins protects against ischemia/reperfusion-induced cardiac injury,” *Circulation*, vol. 122, no. 13, pp. 1308–1318, 2010.

L. Yu, Q. Li, B. Yu et al., “Berberine attenuates myocardial ischemia/reperfusion injury by reducing oxidative stress and inflammation response: role of silent information regulator 1,” *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 1689602, 16 pages, 2016.

G. L. Zhao, L. M. Yu, W. L. Gao et al., “Berberine protects rat heart from ischemia/reperfusion injury via activating JAK2/STAT3 signaling and attenuating endoplasmic reticulum stress,” *Acta Pharmacologica Sinica*, vol. 37, no. 3, pp. 354–367, 2016.

L. Gu, N. Li, W. Yu et al., “Berberine reduces rat intestinal tight junction injury induced by ischemia-reperfusion associated with the suppression of inducible nitric oxide synthesis,” *The American Journal of Chinese Medicine*, vol. 41, no. 06, pp. 1297–1312, 2013.

R. Schmidt, E. Tritschler, A. Hoetzl et al., “Heme oxygenase-1 induction by the clinically used anesthetic isoflurane protects rat livers from ischemia/reperfusion injury,” *Annals of Surgery*, vol. 245, no. 6, pp. 931–942, 2007.

O. Collange, A. L. Charles, E. Noll et al., “Isofluorane preserves liver and lung mitochondrial oxidative capacity after gut ischemia-reperfusion,” *Anesthesia & Analgesia*, vol. 113, no. 6, pp. 1438–1441, 2011.

I. Baoic, D. Weirachra, J. Procknow et al., “Isoflurane favorably modulates guanosine triphosphate cyclohydrolase-1 and endothelial nitric oxide synthase during myocardial ischemia
and reperfusion injury in rats,” *Anesthesiology*, vol. 123, no. 3, pp. 582–589, 2015.

[158] M. Kim, S. W. Park, M. Kim, V. D. D’Agati, and H. T. Lee, “Isolaurane post-conditioning protects against intestinal ischemia-reperfusion injury and multiorgan dysfunction via transforming growth Factor-β1 generation,” *Annals of Surgery*, vol. 255, no. 3, pp. 492–503, 2012.

[159] C. Zhang, L. Zheng, L. Li et al., “Rapamycin protects kidney against ischemia reperfusion injury through recruitment of NKT cells,” *Journal of Translational Medicine*, vol. 12, no. 1, p. 224, 2014.

[160] A. Das, F. N. Salloum, D. Durrant, R. Ockaili, and R. C. Kukreja, “Rapamycin protects against myocardial ischemia-reperfusion injury through JAK2-STAT3 signaling pathway,” *Journal of Molecular and Cellular Cardiology*, vol. 53, no. 6, pp. 858–869, 2012.

[161] A. Kezic, F. Thaiss, J. U. Becker, T. Y. Tsui, and M. Bajecetic, “Effects of everolimus on oxidative stress in kidney model of ischemia/reperfusion injury,” *American Journal of Nephrology*, vol. 37, no. 4, pp. 291–301, 2013.

[162] J. Li, W. T. Chang, C. Q. Li et al., “Baicalin preventive treatment confers optimal cardioprotection by PTEN/Akt/NO activation,” *American Journal of Chinese Medicine*, vol. 45, no. 05, pp. 987–1001, 2017.

[163] A. Liu, L. Huang, H. Fan et al., “Baicalin pretreatment protects against liver ischemia/reperfusion injury via inhibition of NF-kB pathway in mice,” *International Immunopharmacology*, vol. 24, no. 1, pp. 72–79, 2015.

[164] C. C. Lai, P. H. Huang, A. H. Yang et al., “Baicalin attenuates lung injury induced by myocardial ischemia and reperfusion,” *American Journal of Chinese Medicine*, vol. 45, no. 04, pp. 791–811, 2017.

[165] D. Han, J. Wang, S. Ma, Y. Chen, and F. Cao, “SIRT1 as a promising novel therapeutic target for myocardial ischemia reperfusion injury and cardiometabolic disease,” *Current Drug Targets*, vol. 18, no. 15, pp. 1746–1753, 2017.

[166] Q. Zhao, Z. Guo, W. Deng et al., “Calpain 2-mediated autophagy defect increases susceptibility of fatty livers to ischemia-reperfusion injury,” *Cell Death & Disease*, vol. 7, no. 4, p. e2186, 2016.

[167] J. Inserte, V. Hernando, and D. Garcia-Dorado, “Contribution of calpains to myocardial ischemia/reperfusion injury,” *Cardiovascular Research*, vol. 96, no. 1, pp. 23–31, 2012.

[168] S. Li, J. Zhang, Z. Wang et al., “MicroRNA-17 regulates autophagy to promote hepatic ischemia/reperfusion injury via suppression of signal transductions and activation of transcription-3 expression,” *Liver Transplantation*, vol. 22, no. 12, pp. 1697–1709, 2016.

[169] J. Shi, Y. Bei, X. Kong et al., “miR-17-3p contributes to exercise-induced cardiac growth and protects against myocardial ischemia-reperfusion injury,” *Theranostics*, vol. 7, no. 3, pp. 664–676, 2017.

[170] J. Hao, Q. Wei, S. Mei et al., “Induction of microRNA-17-5p by p53 protects against renal ischemia-reperfusion injury by targeting death receptor 6,” *Kidney International*, vol. 91, no. 1, pp. 106–118, 2017.

[171] J. H. Jun, J. W. Song, E. J. Shin, Y. L. Kwak, N. Choi, and J. K. Shim, “Ethyl pyruvate is renoprotective against ischemia-reperfusion injury under hyperglycemia,” *Journal of Thoracic and Cardiovascular Surgery*, vol. 155, no. 4, pp. 1650–1658, 2018.

[172] E. K. Caglayan, K. Caglayan, A. Y. Gocmen et al., “Protective effect of ethyl pyruvate on ischemia-reperfusion injury in rat ovary: biochemical and histopathological evaluation,” *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, vol. 182, pp. 154–159, 2014.

[173] Y. Y. Zhen, C. C. Yang, C. C. Hung et al., “Extendin-4 protects kidney from acute ischemia-reperfusion injury through upregulation of NRF2 signaling,” *American Journal of Translational Research*, vol. 9, no. 11, pp. 4756–4771, 2017.

[174] C. T. Chien, M. J. Jou, T. Y. Cheng, C. H. Yang, T. Y. Yu, and P. C. Li, “Extendin-4-loaded PLGA microspheres relieve cerebral ischemia/reperfusion injury and neurologic deficits through long-lasting bioactivity-mediated phosphorylated Akt/eNOS signaling in rats,” *Journal of Cerebral Blood Flow and Metabolism*, vol. 35, no. 11, pp. 1790–1803, 2015.

[175] G. Hu, Y. Zhang, H. Jiang, and X. Hu, “Extendin-4 attenuates myocardial ischemia and reperfusion injury by inhibiting high mobility group box 1 protein expression,” *Cardiology Journal*, vol. 20, no. 6, pp. 600–604, 2013.

[176] N. Yun, H. I. Cho, and S. M. Lee, “Impaired autophagy contributes to hepatocellular damage during ischemia/reperfusion: heme oxygenase-1 as a possible regulator,” *Free Radical Biology and Medicine*, vol. 68, pp. 168–177, 2014.

[177] X. Chi, N. Guo, W. Yao et al., “Induction of heme oxygenase-1 by hemin protects lung against orthotopic autologous liver transplantation-induced acute lung injury in rats,” *Journal of Translational Medicine*, vol. 14, no. 1, 2016.

[178] J. S. Kim, J. H. Wang, T. G. Bie et al., “Carbamazepine suppresses calpain-mediated autophagy impairment after ischemia/reperfusion in mouse livers,” *Toxicology and Applied Pharmacology*, vol. 273, no. 3, pp. 600–610, 2013.

[179] T. Minor, J. Stegmann, A. Hirner, and M. Koettting, “Impaired autophagic clearance after cold preservation of fatty livers correlates with tissue necrosis upon reperfusion and is reversed by hypothermic reconditioning,” *Liver Transplantation*, vol. 15, no. 7, pp. 798–805, 2009.

[180] T. Minor and A. Paul, “Hypothermic reconditioning in organ transplantation,” *Current Opinion in Organ Transplantation*, vol. 18, no. 2, pp. 161–167, 2013.