REGULATION OF AUTOPHAGY PROTECTS AGAINST LIVER INJURY IN LIVER SURGERY-INDUCED ISCHAEMIA/REPERFUSION

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Abstract
Transient ischaemia and reperfusion in liver tissue induce hepatic ischaemia/reperfusion (I/R) tissue injury and a profound inflammatory response in vivo. Hepatic I/R can be classified into warm I/R and cold I/R and is characterized by three main types of cell death, apoptosis, necrosis and autophagy, in rodents or patients following I/R. Warm I/R is observed in patients or animal models undergoing liver resection, haemorrhagic shock, trauma, cardiac arrest or hepatic sinusoidal obstruction syndrome when vascular occlusion inhibits normal blood perfusion in liver tissue. Cold I/R is a condition that affects only patients who have undergone liver transplantation (LT) and is caused by donated liver graft preservation in a hypothermic environment prior to entering a warm reperfusion phase. Under stress conditions, autophagy plays a critical role in promoting cell survival and maintaining liver homeostasis by generating new adenosine triphosphate (ATP) and organelle components after the degradation of macromolecules and organelles in liver tissue. This role of autophagy may contribute to the protection of hepatic I/R-induced liver injury; however, a considerable amount of evidence has shown that autophagy inhibition also protects against hepatic I/R injury by inhibiting autophagic cell death under specific circumstances. In this review, we comprehensively discuss current strategies and underlying mechanisms of autophagy regulation that alleviates I/R injury after liver resection and LT. Directed autophagy regulation can maintain liver homeostasis and improve liver function in individuals undergoing warm or cold I/R. In this way, autophagy regulation can contribute to improving the prognosis of patients undergoing liver resection or LT.

KEYWORDS
autophagy, cell death, ischaemia/reperfusion, liver resection, liver transplantation

1 | INTRODUCTION

Ischaemia/reperfusion (I/R) initiates a process with transient ischaemia and reperfusion that maintains liver tissue in a microenvironment characterized by anoxia and reoxygenation, which subsequently leads to tissue injury and a profound inflammatory response.¹ Hepatic I/R injury in individuals or animals undergoing liver resection or liver transplantation (LT) may result in liver

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failure with high mortality. Both partial hepatectomy (PH) and LT are effective strategies for treating various liver diseases; however, LT is the only effective strategy for rescuing patients with end-stage liver disease or irreversible liver malignant tumours. Notably, PH and orthotopic LT cause severe complications because they can initiate cell death and hepatic I/R injury. A large number of liver cells die, inducing hypohepatia or even liver failure. In addition, hepatic I/R plays a vital role in the pathophysiology of ischaemic-type biliary lesions since a large number of cholangiocytes undergo apoptosis and necrosis.

In general, I/R can be classified into two types: warm I/R or cold I/R (Figure 1). Warm I/R is observed in patients or animal models undergoing liver resection, haemorrhagic shock, trauma, cardiac arrest or hepatic sinusoidal obstruction syndrome when vascular occlusion inhibits normal blood perfusion in liver tissue. Cold I/R is a condition affecting only patients who have undergone LT because the donated liver graft is preserved in a hypothermic environment prior to entering a warm reperfusion phase. Warm ischaemia induces nutrient depletion, adenosine triphosphate (ATP) depletion and anaerobic glycolysis and promotes the generation of an acidic milieu in the cytoplasm, which subsequently suppresses a myriad of protective enzymes. Although a harsh acidic environment can protect against injury in the liver parenchyma during an acute ischaemic event, severe liver acidosis eventually results in the death of primary hepatocytes after the activation of apoptosis- or necrosis-related pathways. On the other hand, cold ischaemia mainly induces cell death in the sinusoidal endothelium and nonparenchymal cells in liver tissue. Although hypothermia has been shown to reduce energy metabolism and preserve the function of liver grafts, a prolonged ischaemia period and hypothermia lead to cell swelling and liver injury after damaging Na/K ATPase membrane pumps, leading to the accumulation of sodium and chloride. Hypothermia has also been shown to induce a strong adaptive immune response in resected liver grafts characterized by recruitment of T cells into the ischaemic graft. Similarly, liver reperfusion-induced inflammation initiates an innate immune-dominant response in conventional T

**FIGURE 1** Warm I/R or cold I/R initiates three types of cell death: apoptosis, necrosis and autophagy. Hepatic I/R also induces ROS accumulation, the immune response and inflammation at injury sites, which in turn aggravates the death of hepatocytes, sinusoidal endothelial cells and nonparenchymal cells.
lymphocytes, which subsequently leads to injury of both parenchymal and nonparenchymal cells in situ and in liver transplants. Moreover, other inflammatory cells are recruited in the response to hepatic I/R after restoration of blood flow and pH neutralization. In the early stage of reperfusion, resident hepatic macrophages are activated to induce reactive oxygen species (ROS) generation and oxidative stress, while neutrophils are recruited to release inflammatory factors and induce tissue damage at the late stage of reperfusion. Liver I/R also upregulates the release of a cascade of inflammatory factors, including tumour necrosis factor-α (TNF-α), interleukin (IL)-1, IL-2, IL-6 and high mobility group box 1 (HMGB1). Mitochondrial ROS, immune responses and inflammatory factor activation lead to further activation of cell death-related pathways.

Apoptosis, necrosis and autophagy are three main types of cell death in rodents and patients with warm or cold I/R injury. The initiation of apoptosis, necrosis and autophagy may be induced by similar effectors and is usually regulated by similar signalling pathways. Hepatic I/R activates phagocytosis and degradation of apoptotic bodies after cells undergo cell shrinkage, nucleus condensation, chromatin margination and fragmentation of both the nucleus and cytoplasmic structures. This process is determined as apoptosis in cells with normal in appearance. Physiologically, apoptosis is critical for the elimination of damaged or senescent cells and tissue remodelling in injury environments. Apoptosis is initiated either by extrinsic stimuli through cell surface death receptors, including TNF-α, Fas and TNF-related apoptosis-inducing ligand (TRAIL) receptors, or by intrinsic stimuli via a mitochondrial pathway. Thus, activation of caspases leads to cell structure destruction and apoptosis. Compared to apoptosis, pathological necrosis is a disordered and passive cell death in response to acute injury that involves cell bursting but is not generally triggered in normal development. Necrosis progression is typically not associated with the activation of caspases, and the cellular nucleus becomes distended and remains largely intact. The morphologic feature of necrosis is elimination of organelles, formation of large plasma membrane blebs, bleb rupture and subsequent loss of the plasma membrane permeability barrier. Rupture of the plasma membrane promotes the release of cellular contents into the extracellular environment and induces a significant inflammatory response. Under physiological conditions, a relatively low level of autophagy plays a homeostatic role in maintaining cell structures and functions by recycling long-lived proteins and whole organelles. Under stress conditions, autophagy plays a critical role in promoting cell survival and maintaining liver homeostasis by generating new ATP and organelles after degradation of macromolecules and organelles in liver tissue. Activation of autophagy inhibits the progression of caspase-dependent apoptosis, and the activation of caspase-dependent apoptosis inhibits the autophagic process. However, under some conditions, autophagy proceeds to autophagic cell death, which promotes the progression of apoptosis or necrosis in mammals.

Recent studies have highlighted therapies targeting the suppression of I/R injury in liver tissue that rely on complex mechanisms; however, there is a particular emphasis on therapies that control autophagy in liver tissue to reduce inflammation and organ failure. In this review, we comprehensively discuss current strategies and the underlying mechanisms for alleviating I/R injury in liver resection and LT via autophagy regulation. We hope that more investigators will seek to control autophagy regulation specifically to maintain liver homeostasis and improve liver function in individuals undergoing warm or cold I/R. In this way, autophagy regulation will contribute to improving the prognosis of patients undergoing liver resection or LT.

2 | AUTOPHAGY IN LIVER TISSUE

Three main autophagy-related pathways participate in the degradation of cytosolic contents in lysosomes. Macroautophagy facilitates the degradation of entire organelles or parts thereof after the development of a double-membrane autophagosome and the subsequent generation of autolysosomes that degrade cytoplasmic material. Macroautophagy is selectively initiated by organelle injury, and it is upregulated nonspecifically through bioenergetic instability. Microautophagy, which is mediated by acidic organelles such as late endosomes, is the least studied type of autophagy. It is initiated by amino acid starvation. Microautophagy decomposes small autophagic substrates by packaging a cytoplasmic portion into the lumen of a lysosome after the lysosomal membrane is rearranged and develops a protruding arm-like structure. Chaperone-mediated autophagy (CMA) degrades only soluble proteins with a KFERQ motif after binding to heat shock protein family A member 8 (HSPA8) and does not involve vesicle invagination, while biodegradable substrates enter the lysosomal lumen facilitated by a specific spliced isoform of lysosomal-associated membrane protein 2 (LAMP2A). Several injury-causing factors, such as DNA damage, hypoxia and oxidative stress, significantly induce the activation of CMA in mammals. Moreover, CMA is important in the regulation of liver homeostasis because it maintains hepatic metabolism and inhibits tumorigenesis.

Macroautophagy is the predominant form of autophagy and is often referred to as autophagy. Wang et al. highlighted findings showing that reduced autophagic flux is able to impair the adaptive capacity of cells or tissues, enabling them to withstand oxygen damage, including that caused by ischaemia or hypoxia. Komatsu et al. demonstrated that autophagy-related protein (ATG)7 deficiency resulted in enlarged livers in up to 30% of the body of mice and abnormal structures in mitochondria and peroxisomes of hepatocytes. Disabled autophagy in hepatocytes may induce severe hepatic injury since the limited half-life of primary hepatocytes leads to the accumulation of detrimental cellular byproducts. Moreover, autophagy upregulation is initiated to inhibit ROS-induced hepatocellular necrosis after the expression levels of microtubule-associated protein 1 light chain (LC)3-II is upregulated, increasing the number of autophagosomes in liver tissue under partial warm ischaemia without reperfusion. However, inhibition of autophagy by chloroquine treatment aggravates mitochondrial oxidative stress and mitochondrial
dysfunction.\textsuperscript{36} Zhu et al showed that rapamycin (an autophagy activator) effectively downregulated endoplasmic reticulum (ER) stress, inhibited the mechanistic target of rapamycin (mTOR) pathway and enhanced autophagy to protect against liver injury induced by I/R.\textsuperscript{37} However, others have debated whether autophagy activation initiates or aggravates hepatic I/R injury by enhancing liver inflammation. Rapamycin was reported to inhibit liver regeneration and liver weight reconstitution, accompanied by upregulation of inflammatory factors, including TNF-\(\alpha\) and IL-1Ra, but downregulation of hepatocyte growth factor (HGF) and angiogenesis-related factors, including vascular endothelial growth factor receptor 2 (VEGFR2) and angiopoietin, in mice after PH.\textsuperscript{38}

Currently, expert opinion suggests that macroautophagy can be further classified into nonselective autophagy and selective macroautophagy, which targets special organelles or specific compounds for degradation. It is widely accepted that macroautophagy is able to degrade various organelles or substrates, such as mitochondria, the ER, peroxisomes, ribosomes, lipid droplets, iron-based compounds, glycogen, protein aggregates and cytoplasmic pathogens.\textsuperscript{25} Specific names have been ascribed to autophagy of specific compounds, including mitophagy (mitochondria), reticulophagy (ER), pexophagy (peroxisomes), ribophagy (ribosomes), lipophagy (lipids) and ferritinophagy (iron-based compounds).\textsuperscript{39} Reticulophagy effectively maintains the structure and function of the ER via the interaction of diverse receptors with LC3 to generate autophagosomes under various conditions, including starvation, nonalcoholic fatty liver disease (NAFLD), viral infection and fibrosis.\textsuperscript{39} Lipophagy is another important macroautophagic form that is involved in lipid homeostasis and metabolism in liver diseases such as alcoholic liver and nonalcoholic liver diseases, including fibrosis, cirrhosis and hepatocellular carcinoma.\textsuperscript{39} Notably, mitophagy plays a critical role in removing worn-out mitochondria, which have a half-life of 10 to 25 d in healthy liver.\textsuperscript{40} Mitophagy is another important mechanism in which selective abnormally cleaved proteins or damaged mitochondria are eliminated to inhibit the accumulation of mitochondrial-derived ROS and mutated mitochondrial DNA (Figure 2).\textsuperscript{41} Hepatic I/R triggers mitophagy via two distinct pathways: phosphatidylinositol-3-kinase (PI3K)-dependent and PI3K-independent signalling pathways.\textsuperscript{42} Kim et al\textsuperscript{43} demonstrated that inhibition of mitophagy resulted in accumulation of dysfunctional mitochondria, uncoupling of oxidative phosphorylation, ATP depletion and cell death in liver I/R models. Abrogated or inefficient mitophagy may result in uncontrolled ROS accumulation, energy metabolism failure and ultimately cell death in liver tissue.

3 | AUTOPHAGY REGULATION ATTENUATES WARM HEPATIC I/R INJURY

Many previous studies have shown that autophagy upregulation or downregulation exerts protective effects in the attenuation of warm hepatic I/R injury according to the specific circumstances (Table 1). Starvation or ischaemic preconditioning, chemical exposure, plant extract treatment, MSC and/or MSC derivative application, and

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Autophagy and mitophagy contribute to the degradation of organelles to maintain liver function and histology and repair liver injury in hepatic I/R.}
\end{figure}
| Animal | Time | Treatment | Autophagy regulation | Effect | Mechanism | Ref. |
|--------|------|-----------|---------------------|--------|-----------|------|
| Mouse  | Pretreatment | Short-term starvation | ↑ | Decrease serum aminotransferases levels; decrease hepatocyte apoptosis; attenuate pathological damage | Upregulate the expression of SIRT1; inhibit hepatocellular apoptosis | 44 |
| Mouse  | Pretreatment | IP | ↑ | Alleviate liver I/R injury; decrease serum levels of aminotransferases, inflammatory cytokines; reduce histopathologic changes | Activate autophagy and the HO-1-mediated signalling pathway | 45 |
| Mouse  | Pretreatment | RIP | ↑ | Decrease the incidence of hepatocyte necrosis, ballooning degeneration and sinusoidal congestion; reduces Suzuki’s score | Increase HO-1 expression; activate the ERK1/2 and p38-MAPK pathways | 46 |
| Mouse  | Pretreatment | Cisplatin | ↑ | Reduce I/R-induced ALT level and liver damage | Prevent the release of HMGB1; decrease liver I/R-induced inflammatory mediator production | 49 |
| Mouse  | Pretreatment | ATRA | ↑ | Diminish levels of ALT and AST; decrease the degree of histopathological changes | Inhibit apoptosis and inflammation | 50 |
| Mouse  | Pretreatment | Amiodarone | ↑ | Improve hepatocyte proliferation; increase the survival rate of PH mice | Remove damaged mitochondria; mTOR-independent signalling | 51 |
| Mouse  | Pretreatment | ATG7 knockdown or chloroquine | ↓ | Aggravated liver injury; reduce liver growth and hepatocyte proliferation | Increase the number of dysfunctional mitochondria | 51 |
| Rat    | Pretreatment | Lithium | ↑ | Decrease levels of ALT and AST | Decrease neutrophil infiltration; decrease production of inflammatory mediators; decrease HMGB1 expression and release; prevent dephosphorylation of GSK-3β; decrease hepatic apoptosis | 52 |
| Mouse  | Pretreatment | Spermidine | ↑ | Decrease levels of serum transaminases; decrease release of inflammatory cytokines; inhibit histopathological changes | Inhibit liver apoptosis; alleviate I/R-induced inflammation; activate the AMPK-mTOR-ULK1 signalling pathway | 53 |
| Mouse  | Pretreatment | NAC | ↑ | Decrease levels of ALT and AST; attenuate pathological changes | Attenuate JNK-mediated signalling pathway activation; inhibit the expression of Bax, TNF-α, NF-κB, IL2, IL6 | 54 |
| Mouse  | Pretreatment | Vitamin D | ↑ | Preserve liver function; reduce histological damage | Ameliorate oxidative stress; attenuate inflammation; decrease the levels of TNF-α, IL-6 and IL-2; increase the IL-10 level | 55 |
| Mouse  | Pretreatment | Antecedent tri-iodothyronine | ↑ | Preserve liver function; decrease apoptosis rate; reduce histological damage | Upregulate the MEK/ERK/mTORC1 signalling pathway; enhance antioxidative stress; attenuate neutrophil infiltration | 56 |
| Rat    | Pretreatment | Baicalein | ↑ | Blunt elevation of ALT and AST levels; attenuate histological changes | Upregulate HO-1 expression | 57 |

(Continues)
| Animal           | Time        | Treatment     | Autophagy regulation | Effect                                                                 | Mechanism                                                                                     | Ref.  |
|------------------|-------------|---------------|----------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------|
| Mouse            | Pretreatment| Shikonin      | ↓                    | Reduce serum AST and ALT levels; improve pathological features; reduce hepatocyte apoptosis rate | Decrease the expression of Bax, caspase 3 and caspase 9; reduce the release of IL-1β, TNF-α and IL-6; activate the PI3K/Akt signalling pathway | 58    |
| Mouse            | Pretreatment| OA            | ↑                    | Improve tolerance to hepatic I/R injury                                  | Decrease phosphorylation of AKT; decrease p65 nuclear translocation; downregulate oxidative stress | 59    |
| Mouse            | Pretreatment| OA            | ↓                    | Downregulate ALT and AST levels; improve histology                       | Inhibit phosphorylation of JNK; decrease the expression of HMGB1 and TNF-α; inhibit apoptosis  | 60    |
| Mouse            | Pretreatment| Bergenin      | ↓                    | Alleviate liver function injury; inhibit liver IR-induced apoptosis       | Eliminate ROS; inhibit the release of inflammatory factors; activate the PPAR-γ signalling pathway | 61    |
| Mouse            | Pretreatment| Salidroside   | ↓                    | Ameliorate hepatic I/R injury                                            | Downregulate phosphorylation of P38, JNK and ERK to suppress pathway activation; inhibit the MAPK signalling pathway; inhibit the release of IL-6 and TNF-α; reduce the hepatocyte apoptosis rate | 62    |
| Mouse            | Pretreatment| Astaxanthin   | ↓                    | Ameliorate hepatic I/R injury involving liver enzyme pathology           | Inhibit the release of ROS and inflammatory cytokines; reduce the release of inflammatory factors including TNF-α and IL-6; reduce the Bax/Bcl-2 ratio; attenuate ROS/MAPK signalling pathway activation | 63    |
| Mouse            | Pretreatment| Quercetin     | ↓                    | Ameliorate hepatic I/R injury; inhibit apoptosis                         | Inactivate the ERK/NF-κB signalling pathway; inhibit the release of TNF-α and IL-6             | 64    |
| Mouse            | Pretreatment| Levo-tetrahydropalmatine | ↓ | Alleviate I/R injury                                                      | Inhibit ERK/NF-κB-mediated hepatocyte apoptosis; downregulate the release of TNF-α and IL-6 | 65    |
| Rat              | Pretreatment| MSCs          | ↑                    | Decrease hepatocellular necrosis and cytoplasmic vacuolization; decrease ALT and AST levels | Upregulate HO-1 expression                                                                  | 66    |
| Porcine          | Posttreatment| MSCs          | ↓                    | Decrease serum levels of AST, ALT, total bilirubin and lactate dehydrogenase | Attenuate oxidative stress; suppress the generation of myeloperoxidase and malonaldehyde     | 67    |
| Mouse            | Posttreatment| Rapamycin pretreated MSCs | ↑ | Enhance recovery of hepatic function; attenuate pathological changes     | Attenuate the inflammatory response; reduce oxidative stress; enhance MSC homing via the CXCR4/CXCL12 axis | 68    |
| Rat              | Posttreatment| HSP-MSCs      | ↑                    | Improve histopathology; reduce Suzuki scores                             | Increase the homing and survival rate of transplanted MSCs                                   | 69    |
| Mouse            | Pretreatment and posttreatment| MSC-Heps-Exo | ↑ | Decrease serum levels of liver enzymes                                   | Decrease hepatocyte apoptosis rate                                                             | 70    |
| Mouse            | Pretreatment| KO of ATG5    | ↓                    | Impair recovery of liver regeneration; attenuate DNA synthesis; decrease liver hypertrophy and hepatocyte senescence | Suppress autophagy activity and mitochondrial oxidation                                       | 71    |

TABLE 1 (Continued)
gene modification contribute to maintaining liver homeostasis and liver function in warm hepatic I/R models and patients via autophagy regulation and related mechanisms.

3.1 | Starvation or ischaemic preconditioning

I/R initiates liver injury through transient ischaemia and reperfusion; intriguingly, preconditioning tissue with starvation or ischaemia effectively protects against liver injury. Short-term starvation through calorie restriction or fasting has been shown to exert beneficial effects on multiple organs and preserve organ function under stress conditions. Short-term starvation protects against liver I/R injury, as evidenced by lower levels of serum aminotransferases and hepatocyte apoptosis and improved pathological damage in mouse models. Furthermore, starvation significantly upregulated hepatocellular autophagy and the expression of the longevity gene silent information regulator factor 2-related enzyme 1 (SIRT1) in I/R-treated liver tissue.\textsuperscript{44} Investigators pretreated mice with transient ischaemia (10–15 min) in liver tissue around the portal triad by occluding of hepatic inflow by applying a vascular clamp, and then, they removed the clamp to cause transient reperfusion (10–15 min). Ischaemic preconditioning (IP) significantly activated autophagy and the haem oxygenase (HO)-1-mediated pathway to ameliorate hepatic I/R injury, as indicated by the downregulation of aminotransferases and inflammatory cytokine release and the reduction in histopathologic changes in the liver tissue.\textsuperscript{45} Remote ischaemic preconditioning (RIPC) is defined as transient ischaemia in distant tissues or organs such as a limb or intestine to protect liver tissue from I/R-induced injury. RIPC is applied to limbs through induced ischaemia for dozens of minutes, followed by dozens of minutes of reperfusion prior to long-term ischaemia. RIPC has been shown to protect the liver from I/R injury by inducing HO-1/p38-mitogen-activated protein kinase (MAPK)-dependent autophagy.\textsuperscript{46} Although various experimental studies showed pronounced benefits of IP for liver surgery, a meta-analysis showed that IP failed to improve the prognosis of patients after liver resection or LT.\textsuperscript{47,48}

3.2 | Chemicals

Autophagy activation, inhibition of inflammation or inhibition of oxidative stress has been reported to improve liver function and the prognosis of I/R injury. During hepatic I/R, injured sites showed significantly upregulated the expression of Beclin-1 and ATG8/LC3 indicating the formation and expansion of autophagosomes in vivo to protect against hepatic I/R-induced injury. Administration of nontoxic concentrations of cisplatin notably increased mitophagy levels and prevented the release of HMGB1 induced by hepatic I/R, which subsequently attenuated liver injury.\textsuperscript{49} All-trans retinoic acid (ATRA) is effective in protecting the liver from I/R injury by enhancing autophagy in a forkhead box class O (FOXO)3/p-AKT/FOXO1 signalling-dependent manner.\textsuperscript{50} Lin et al. demonstrated
that amiodarone significantly improved hepatocyte proliferation, liver tissue growth and the survival rate of PH mice by upregulating autophagy and eliminating damaged mitochondria. Before 60 min of partial warm ischaemia, chronic lithium treatment significantly reduced I/R-induced liver injury by inducing liver autophagy and reducing hepatic inflammatory cytokine levels, neutrophil infiltration and HMGB1 release. Similarly, spermidine pretreatment significantly attenuated liver apoptosis, the levels of serum transaminases and histopathological changes via upregulation of AMP-activated protein kinase (AMPK)-mTOR-unc-51 like kinase 1 (ULK1)-dependent autophagy and downregulation of inflammatory cytokines. N-acetylcysteine (NAC) has been reported to prevent I/R injury by inducing autophagy after attenuation of the c-Jun N-terminal kinase (JNK)-mediated signalling pathway and downregulation of Bax, TNF-α, nuclear factor-kappaB (NF-κB), IL-2 and IL-6. Vitamin D significantly preserved liver function and decreased histological damage via amelioration of oxidative stress and upregulation of autophagic flux. However, inhibition of the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway or phosphatase and tensin homolog (PTEN)/PI3K/AKT/mTOR pathway partially abolished the protective effect of vitamin D in hepatic I/R mice, and knockdown of Beclin-1 completely reversed the protection conferred by vitamin D. On the other hand, antecedent triiodothyronine injection significantly preserved liver function, decreased the apoptosis rate, reduced histological damage and enhanced anti-oxidative stress in hepatic I/R mice by upregulating MEK/ERK/mTORC1-mediated autophagy. This study indicates that targeting autophagy regulation by chemicals is vital in the protection of hepatic I/R-induced injury.

### 3.3 Plant extracts

A large amount of evidence has shown that activation of autophagy by plant extract treatment contributes to liver protection via the activation of different signalling pathways. Baicalein pretreatment blunted an increase in alanine transaminase (ALT) and aspartate aminotransferase (AST) and alleviated histological changes via induction of autophagy and upregulation of HO-1 expression. Shikonin pretreatment reduced serum transaminase levels and attenuated pathological features by upregulating PI3K/AKT-mediated autophagy but decreasing the expression of apoptosis-related proteins, including Bax, caspase-3 and caspase-9. Pretreatment with oleic acid (OA) improved the tolerance of mice undergoing hepatic I/R injury by downregulating the phosphorylation of AKT and oxidative stress. An in vitro study showed that OA effectively inhibited oxidative stress, inflammation and cell death in hydrogen peroxide (H₂O₂)-treated HepG2 cells by upregulating autophagy.

Other investigations showed that plant extract pretreatment attenuated hepatic I/R injury via induction of autophagy and apoptosis. Pretreatment with OA for 7 consecutive days prior to PH notably alleviated liver injury by downregulating caspase-3, caspase-9, Bax, Beclin-1 and LC3 and inhibiting JNK, HMGB1 and TNF-α in hepatic I/R mice. Bergenin pretreatment significantly decreased the levels of liver enzymes by inhibiting autophagy and apoptosis, and reducing the levels of mitochondrial ROS and inflammatory factors such as TNF-α, IL-6 and IL-1β. At the molecular level, bergenin pretreatment upregulated the PPAR-γ pathway but downregulated the phosphorylation of P38 MAPK, NF-κB and Janus kinase 2 (JAK2)/signal transducer and activator of transcription 1 (STAT1) pathways in a dose-dependent manner. Pretreatment with salidroside or astaxanthin significantly inhibited the release of ROS and inflammatory cytokines via inactivation of P38 MAPK, JNK and ERK and inhibition of autophagy and apoptosis in hepatic I/R mouse models. Quercetin and levo-tetrahydropalmatine (L-THP) preconditioning also conferred protection against hepatic I/R injury and inhibited the release of inflammatory cytokines via inactivation of the ERK/NF-κB pathway and inhibition of autophagy and apoptosis.

### 3.4 MSCs and derivatives

Recently, the application of mesenchymal stem cells (MSCs) has been a hot topic in regenerative medicine used to treat various diseases. These cells and their derivatives are able to enhance liver regeneration and liver function via their migration, differentiation, anti-inflammation, antioxidation and immunoregulation capacities. MSCs mitigate I/R injury via upregulation of HO-1 expression and autophagy in vivo, while the autophagy inhibitor 3-methyladenine or HO-1 zinc protoporphyrin IX significantly reverses the protective effects of MSCs. Ge et al. documented that MSCs effectively enhanced liver function in PH porcine models by attenuating oxidative stress and autophagy, as demonstrated by the reduction in autophagy markers such as Beclin-1, ATG5, ATG12 and LC3II and upregulation of P62. Rapamycin is able to enhance MSC migrative and anti-inflammatory capacities without affecting MSC viability in vitro. Rapamycin pretreatment enhanced MSC migration into injured liver sites and subsequently improved hepatic performance, attenuated pathological changes and suppressed the release of inflammatory cytokines in a liver I/R mouse model.热 shock pretreatment (HSP) for 2 h reduced the apoptosis rate of MSCs, as evidenced by downregulation of Bax and cytochrome C and upregulation of Bcl-2 and autophagy in H₂O₂-treated MSCs. Administration of HSP-pretreated MSCs significantly decreased the levels of serum aminotransferases, lowered Suzuki scores and increased the survival rate in I/R animal models via activation of the p38MAPK/mTOR pathway. In addition to MSCs, their derivatives, such as hepatocyte-like cells or exosomes, contribute to liver protection via autophagy regulation. MSC-derived hepatocyte-like cell exosomes (MSC-Heps-Exos) significantly inhibited hepatocyte apoptosis and reversed hepatic I/R injury in vitro and in vivo by upregulating autophagic flux.
Multiple studies have demonstrated that gene modification with autophagy inhibition aggravates liver injury, while autophagy enhancement protects against I/R injury. Knockdown of ATG7 aggravates hepatic I/R injury and inhibits liver regeneration by abrogating autophagy and damaging mitochondria. Knockdown of ATG5 promotes the release of senescence-associated factors, including IL-6 and IL-8, and aggravates PH-induced injury in mice by impairing autophagy and upregulating the expression levels of hepatic P62 and P21.72 Parkinson KO induced cell cycle arrest and aggravated DNA damage via suppression of mitophagy and promotion of hepatocyte apoptosis, leading to reduced hepatocyte survival in a hepatic I/R model.72 Overexpression of miR-1907 in mice led to a significantly higher liver weight/body weight ratio in PH-treated mice by activating autophagy and enhancing hepatocyte proliferation and liver regeneration.74 However, several studies have demonstrated that activation of autophagy aggravates hepatic I/R injury, while inhibition of autophagy protects against PH-induced injury. Overexpression of mTOR enhances autophagic flux and activated the transcription-3 pathway, which subsequently reduces liver injury and warm reperfusion promotes the regeneration and recovery of liver grafts.80

### Table 2: Autophagy regulation protects liver grafts from I/R injury and rejection

| Animal | Time | Treatment | Autophagy regulation | Effect | Mechanism | Ref. |
|--------|------|-----------|----------------------|--------|-----------|------|
| Rat    | Posttreatment | PI3K inhibitors, wortmannin or LY294002 | ↓ | Reduce liver damage and the mortality rate of recipient rats | Inhibit autophagy | 77 |
| Rat    | Pretreatment | 3-MA | ↓ | Prolong liver graft survival in rats after LT; reduce rejection | Reduce function of CD8+ T cells; accelerate the apoptosis of CD8+ T lymphocytes | 78 |
| Mice and human | Pretreatment | Antibiotic | ↑ | Improve hepatocellular function; decrease incidence of early allograft dysfunction | Downregulate CHOP and inflammation | 79 |
| Rat    | Pretreatment | Berberine | ↑ | Restore liver function; preserve liver histology | Attenuate oxidative stress and apoptosis; activate the SIRT1/FoxO3a signalling pathway | 80 |
| Rat    | Pretreatment | HO-1-overexpressing MSCs | ↑ | Decrease histopathological characteristics and rejection activity index of transplanted liver | Activate the ERK/mTOR signalling pathway | 81 |
| Mouse and human | Pretreatment | HO-1-overexpressing macrophages | ↑ | Decrease LT-induced liver damage | Upregulate SIRT1/LC3B expression; promote anti-inflammation; attenuate hepatocellular death; enhance SIRT1/LC3B expression | 82 |

Liver grafts in animal models and patients undergoing LT are challenged by exposure to cold ischaemia/warm reperfusion (CI/WR), which subsequently disrupts the sinusoid. The critical role of autophagy regulation in LT is the protection of liver grafts from I/R injury and rejection (Table 2). Then, upregulated autophagy results in massive necrosis of hepatocytes within 2 h without activation of caspase-3 or caspase-7. However, the PI3K inhibitors wortmannin and LY294002 effectively reduced liver damage and the mortality rate of recipient rats via suppression of autophagy.77 It has also been reported that autophagy inhibition contributes to the regulated activity of T cells and immune regulation in LT models. Chen et al. demonstrated that autophagy inhibition in LT models significantly prolonged the activation of CD8+ T cells. They indicated that autophagy inhibition in immune regulation autophagy 3- methyladenine (3-MA) of CD8+ T cells and immune regulation autophagy 3- methyladenine (3-MA) autophagy inhibitors, wortmannin or LY294002 effectivly reduced liver damage and the mortality rate of recipient rats.
Antibiotics may serve as therapeutic targets in LT by upregulating autophagy and downregulating ER stress and inflammation. Antibiotic pretreatment attenuated hepatic I/R injury in mouse allogeneic OLTs via the gut-liver axis. Nakamura et al. showed that antibiotic pretreatment improved liver function, decreased the incidence of early allograft dysfunction, and mitigated I/R injury in mice after LT by upregulating the levels of PGE2 receptor 4 (EP4) and LC3B but decreasing CCAAT/enhancer-binding protein homologous protein (CHOP) levels. Berberine, a traditional Chinese medicine, restored liver function and preserved liver histology in rats after LT through the upregulation of SIRT1/FOXO3α-mediated autophagy and attenuation of liver-specific oxidative stress and apoptosis.

5.2 | Autophagy regulation in aged liver grafts with hepatic I/R injury

Cell and tissue ageing is a normal phenomenon in elderly people, and it is closely related to the high incidence and severity of diseases in this population. Ageing has been associated with elevated levels of ALT, AST, lipofuscin accumulation, steatosis, fibrosis and defective liver regeneration after PH. In addition, ageing is often associated with reduced autophagic flux and lower liver regeneration capacity. In elderly patients, ageing liver tissue shows slow hepatic blood flow and decreased quantities of mitochondria and endoplasmic reticula, which results in poorer regeneration after PH and LT. In comparison to 8- to 12-week-old mice, 12- to 13-month-old mice presented more severe liver damage and higher liver inflammatory responses when exposed to 90 min of warm ischaemia and 8 h of reperfusion. Older mice showed decreased liver reperfusion, as shown by decreased levels of HGF, c-Met, cyclin D1, cyclin A2, proliferation cell nuclear antigen (PCNA) and SMP30, compared with young mice after PH. The dysfunction of liver regeneration and inhibition of autophagy in the older mice resulted in a decreased liver weight/body weight ratio and lower survival rate. Ageing livers undergoing hepatic I/R showed decreased mitophagy and depletion of Parkin in mice, while enhanced mitophagy more effectively protected livers against I/R injury. Liu et al. demonstrated that administration of plasma from young rats enhanced liver tissue restoration in old rats after hepatic I/R injury via activation of AMPK/ULK1-mediated autophagy. The combination of ischaemia and rapamycin pretreatment protected old livers from I/R injury, as demonstrated by improved liver function and liver histology, and the protection was mediated by upregulation of autophagic flux in aged mice in vivo. It has been reported that one of the most important autophagy-related proteins, ATG4β, is lost in aged livers, and overexpression of ATG4β reversed autophagy inhibition and subsequently reduced hepatic I/R injury in 26-month-old mice. This study shed light on autophagy enhancement in improving the prognosis of older patients undergoing PH or LT.

5.3 | Autophagy regulation in steatotic liver grafts with hepatic I/R injury

Steatotic livers are more sensitive to liver resection or LT-induced hepatic I/R, which results in an increased risk of postoperative complications. Along with mitochondrial dysfunction, ER stress and inflammation after hepatic I/R, lipid accumulation and large cell volume, which obstructs the adjacent sinusoid space, result in reduced delivery of oxygen and nutrients, which contributes to hepatic I/R injury in steatotic livers. The impairment of autophagy in steatotic liver aggravated liver injury induced by cold I/R in steatotic rat livers, while pretreatment with the autophagic stimulator simvastatin effectively attenuated I/R-induced liver injury. Simvastatin pretreatment effectively protects against microcirculation deterioration and...
endothelial dysfunction in moderately steatotic livers during cold storage and warm reperfusion via an NO-mediated mechanism.\textsuperscript{95}

On the other hand, the combined action of melatonin and trimetazidine significantly improved the liver function of steatotic liver grafts preserved in Institut Georges-Lopez (IGL)-1 solution via AMPK activation, autophagy activation and ER stress inhibition.\textsuperscript{96} With relevance to the prognosis of patients after LT and those with steatotic livers, hypothermic reconditioning (HR), which is implemented by insufflation of gaseous oxygen, notably improved graft function by attenuating mitochondrial dysfunction and restoring hepatocellular autophagy in rats.\textsuperscript{97} Domiat et al\textsuperscript{98} demonstrated that IP before prolonged ischaemia decreased hepatocyte necrosis and liver dysf

6 CONCLUSION

In general, activation of autophagy is recognized as a mechanism that confers protection against hepatic I/R injury, while excessive autophagy is acknowledged for its role in accelerating the apoptosis of hepatocytes and/or liver nonparenchymal cells. It is widely accepted that stimulation of autophagy generally promotes liver regeneration and inhibits liver dysfunction, although the pathogenesis of warm and cold liver I/R injury is consistent with the complex interplay between autophagy, necrosis and apoptosis. Autophagy initiation is a potential mechanism to improve hepatocyte survival in patients after warm or cold I/R because it degrades intracellular components and eliminates organelle and protein waste. However, the results of studies on autophagy regulation during warm and/or cold liver I/R remain discordant. A fraction of studies documented downregulation of autophagy in protecting against warm or cold liver I/R injury via inhibition of inflammation and cellular apoptosis and necrosis. The dual role of autophagy suggests that upregulation or downregulation of autophagy may be an effective treatment strategy for the inhibition of liver damage. Autophagy regulation with gene modification in animal models provides a specific strategy to modify the expression of autophagic proteins and therefore is as an effective treatment to preserve liver function in hepatic I/R models. We suggest that future studies focus on clarifying the autophagy regulation mechanism in liver grafts from specific populations eligible for LT, which will contribute to increasing the LT rate and decreasing the low graft function rate in patients with end-stage liver diseases.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Chenxia Hu: Validation (equal); Writing-review & editing (lead).

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DATA AVAILABILITY STATEMENT

Not applicable.

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