Ischemia-reperfusion injury (IRI) is considered an inherent component involved in liver transplantation, which induce early organ dysfunction and failure. And the accumulating evidences indicate that the activation of host innate immune system, especially hepatic macrophages, play a pivotal role in the progression of LIRI. Inflammasomes is a kind of intracellular multimolecular complexes that actively participate in the innate immune responses and proinflammatory signaling pathways. Among them, NLRP3 inflammasome is the best characterized and correspond to regulate caspase-1 activation and the secretion of proinflammatory cytokines in response to various pathogen-derived as well as danger-associated signals. Additionally, NLRP3 is highly expressed in hepatic macrophages, and the assembly of NLRP3 inflammasome could lead to LIRI, which makes it a promising therapeutic target. However, detailed mechanisms about NLRP3 inflammasome involving in the hepatic macrophages-related LIRI is rarely summarized. Here, we review the potential role of the NLRP3 inflammasome pathway of hepatic macrophages in LIRI, with highlights on currently available therapeutic options.

Keywords: inflammasome, NLRP3, ischemia reperfusion injury, hepatic macrophage, liver transplantation

INTRODUCTION

The innate immunity acts as the first line of defense that recognizes and eradicates pathogens in human. It is implemented in the presence of pathogen-associated molecular patterns (PAMPs) (such as bacteria, viruses and parasites) or damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs) (1–4). In the past decades, various kinds of PRRs (inflammasomes) were discovered in succession, such as Nod-like receptor protein 1 (NLRP1), NLRP2, NLRP3, absent in melanoma 2 (AIM2) and NLR family CARD domain containing 4 (NLRC4) (5, 6). As the most well studied inflammasome, NLRP3 has been confirmed to be a critical component that mediates caspase-1 activation and cleavage of gasdermin D (GSDMD) in response to microbial infection and specific endogenous danger-related stimuli (7–11). Activated GSDMD...
facilitate the formation of pore in the plasma membrane and trigger the pyroptotic cell death and enhance the secretion of inflammatory cytokines including IL-1β and IL-18 (12).

At present, liver transplantation (LT) is widely used as the most effective and definitive treatment for end-stage liver diseases, hepatic malignancies, acute fulminant hepatic failure, and metabolic disorders (13). During the LT surgery, the cell death in donor liver was exacerbated following the restoration of oxygen delivery. This special pathological disorder is considered as liver ischemia reperfusion (I/R) injury (LIRI) (14). Due to the death in donor liver was exacerbated following the restoration of oxygen and nutrient interruption. And this period is called ischemia stage. Then extended ischemia duration would lead to substantial parenchymal cell death. The other stage is reperfusion stage, in which the innate immunity and sterile inflammatory response are intensified. The macrophages in liver such as Kupffer cells (KCs) can be activated and play an important role in the context of LIRI (15). Recent studies have demonstrated that blocking the local inflammatory response in liver could effectively reduce LIRI. Thus, it is necessary to explore the potential strategies to prevent the innate immunity and inflammatory response activation during LIRI.

This review summarizes the recent advances in our understanding of the activation and regulation of the NLR3 inflammasome activation, as well as its role in LIRI with highlights on the prevention of LIRI by inhibiting NLR3 inflammasome aberrant activation.

THE NLR3 INFLAMMASOME

The NLR3 inflammasome complex consists of an amino-terminal pyrin domain (PYD), a central nucleotide-binding and oligomerization domain (NOD), and a C-terminal leucine-rich repeat (LRR) domain (7, 16, 17). The pyrin domain of NLR3 frequently referred to apoptosis-associated speck-like protein (ASC), which initiates the assembly of inflammasome.

The NLR3 inflammasome can be activated by a wide range of stimuli that include Candida albicans, bacteria that produce pore-forming toxins such as Staphylococcus aureus and Listeria monocytogenes, viruses (such as influenza virus) (5, 18). Moreover, it is identified that host-derived molecules (including extracellular ATP, hyaluratan, fibrillar amyloid-β peptide, extracellular glucose, monosodium urate (MSU) crystals, and uric acid etc.) are involved in the NLR3 inflammasome activation (18). On the basis of structural and chemical differences between these stimuli, it is suggested that NLR3 senses common cellular events induced by its stimuli, but does not directly bind to it. However, there is still no strong evidence to support this hypothesis. Currently, a two-signal model has been proposed for NLR3 inflammasome activation. The first signal is responsible for initiating the NLR3 inflammasome, which including microbial components or endogenous cytokines. The second signal from pore-forming toxins, extracellular ATP, or particulate matter activates the NLR3 inflammasome.

The excessive molecular and cellular signaling events have clearly recognized as the major consequences of NLR3 stimuli, compromising reactive oxygen species (ROS), mitochondrial dysfunction, lysosomal damage, and ionic flux (10, 19). Proposed as the common signal for NLR3 inflammasome activation, it is observed that the level of ROS increased after the NLR3 stimuli treatment. Lysosomal NADPH oxidase is deemed to be the origin of ROS generation, and the accumulation process of ROS may be caused by respiratory function, which is closely related to the activation of inflammasome. Furthermore, it is illustrated that mitochondrial ROS (mtROS) is also a kind of production in dysfunctional mitochondria (20). As an essential element, mtROS can be continuously increased with the release of LPS and ATP and mitochondrial DNA (mtDNA) into the cytoplasm. This process is important for the mtROS-dependent manner of NLR3 inflammasome activation. Furthermore, some kinds of particulate matter (such as MSU, alum, silica, asbestos, amyloid-β, cholesterol crystals, and calcium crystals) induces NLR3 inflammasome activation in macrophages. Moreover, lysosomal damage after phagocytosis results in the leakage of lysosomal contents into the cytosol. However, the mechanism involves in lysosomal disruption to NLR3 inflammasome activation remains unclear. Lysosomal acidification, leakage of active lysosomal enzymes such as Cathespins B, L, C, S, and X may account for NLR3 inflammasome activation. The ionic flux events, such as K⁺ efflux, Ca²⁺ mobilization, Cl⁻ efflux, and Na⁺ influx, could all be accelerated by NLR3 stimuli, which are implicated in maintaining the NLR3 inflammasome activity (Figure 1).

HEPATIC MACROPHAGE PARTICIPATING IN LIRI

Hepatic macrophages play an important role in the pathogenesis of LIRI and have been proposed as the primary cells for NLR3 activation (15). Recent studies have revealed that hepatic macrophages are a heterogeneous population of innate immune cells. According to the molecular characteristics, hepatic macrophages can be categorized into liver-resident (KCs and liver capsular macrophages (LCMs)) and non-resident (monocyte-derived and peritoneal macrophages) cells (15).

KCs account for 20%~35% of all non-parenchymal cells in the liver and 80%~90% of tissue macrophages presented in the body. KCs are marked as CD45⁺ F4/80⁺ CD11b⁻ /low CLEC4F⁺ cells in mice (21). Analyzing the single-cell RNA-sequencing data, the researchers identified two distinct subtypes of KCs in liver: the immunoregulatory KCs and the pro-inflammatory KCs (22).

Act as the microenvironment sensor, KCs resides at the luminal side of the hepatic sinusoidal endothelium. They are essential for maintaining local homeostasis, such as clearance of pathogens of systemic and gut origin, and regulation of iron...
metabolism. KCs play a vital role in the liver homeostasis by utilizing followed functions: (i) clearance of metabolic waste and cellular debris (22–24); (ii) preservation of iron homeostasis via engulf of red blood cells and the subsequent recycling of iron (25–28); (iii) regulation of cholesterol metabolism through the production of cholesteryl ester transfer proteins (29); (iv) mediation of antimicrobial defense (30, 31) and (v) promotion of immunological tolerance.

LCMs are newly identified murine liver-residents of the CD11b+F4/80+CX3CR1+MHC II+ phenotype. LCMs do not express classic Kupffer cell (TIM4 and CLEC4F) or monocyte-derived macrophage (Ly6C) markers and form a contiguous cellular network in the hepatic capsule (23). LCMs sense peritoneal bacteria and promote recruitment of neutrophil into the capsule. When LCMs populated in the hepatic sinusoids, they are responsible for monitoring the expansion of intra-peritoneal bacteria. In order to avoid the exhaustion of LCMs, blood monocytes could supply and mature LCMs in the steady-state. Despite the growing recognition of the importance of LCMs in hepatic pathogen defense, whether LCMs play a role in LIRI-induced sterile inflammation in the liver remains unclear and needs to be further addressed.

Monocyte-derived macrophages (MoMφs) are differentiated from bone marrow (BM) CX3CR1+CD117+Lin− progenitor cells-derived circulating monocytes. In mice, MoMφs are CD11b+, F4/80intermediate (int), Ly6C + and CSF1R+ while KCs are CD11blow, F4/80high and Clec4F+ (21, 24). Hepatic MoMφs could be classified into two main subpopulations based on the Ly6C expression: Ly6C high and Ly6C low MoMφs in mouse models of liver diseases. Based on the recent single-cell RNA-sequencing results, it is illustrated that CD68+MARCO+ KCs, CD68+MARCO− macrophages, and CD14+ monocytes are specifically enriched in the liver microenvironment (26). Through the further integrative analysis, it is also found that CD68+MARCO+ KCs could be recognized by immune tolerance (e.g., VSIG4) and inflammation inhibiting (e.g., CD163 and HMOX1) related genes. CD68+MARCO− macrophages as recruited proinflammatory macrophages show significantly proinflammatory responses than both CD68− MARCO− macrophages and hepatic CD14+ monocytes.

In the steady environment, KCs self-renew via homeostatic repopulation (27). Under cellular stress, the self-renewal of KCs...
would be hampered, which results in the suppression of their homeostatic repopulation. Sterile inflammation (such as LIRI) decrease KC numbers, which would be replaced by bone marrow-derived monocytes replacing in a mouse LIRI model (28). Notably, infiltrating Ly6C<sup>high</sup>-CCR2<sup>high</sup>-CX3CR1<sup>low</sup> monocyte-derived macrophages (MoMFs) show great plasticity maintaining phenotype and functions. In mouse models after depletion of Kupffer cell by diphtheria toxin receptor (DTR), MoMFs accumulate the hepatic macrophage differentiated towards functional and self-renewing KCs (21).

Since their depletion promotes liver inflammation, KCs undergoing cell death in response to LIRI may affect homeostasis and activate inflammatory macrophage in mice (28). Being in contact with DAMPs produced by dead or moribund LIRI-stressed cells, KCs are activated through sensing early organ damage via PRRs (Figure 2). Then these activated KCs secrete cytokines and chemokines that recruit circulating monocytes, neutrophils and T cells to promote liver injury (29). Liver sterile inflammation recruits new populations of extrahepatic macrophages (emergency repopulation) such as MoMFs and peritoneal macrophages. These monocytes consist of a bone marrow-derived pro-inflammatory Ly6C<sup>high</sup>-CCR2<sup>high</sup>-CX3CR1<sup>low</sup> subset and an anti-inflammatory Ly6C<sup>low</sup>-CCR2<sup>low</sup>-CX3CR1<sup>high</sup> subset in mice (27). Human monocytes are similarly defined as CX3CR1<sup>low</sup> CD14<sup>+CD11b<sup>high</sup>CD11c<sup>low</sup>CD62L<sup>-CD16<sup>low</sup></sup> or CX3CR1<sup>high</sup> CD14<sup>low</sup>CD16<sup>low</sup>CD11b<sup>high</sup>CD11c<sup>high</sup> subsets. In summary, the above hepatic macrophages play a proinflammatory effect after sensing DAMPs and mediate pathogenesis in LIRI.

**The NLRP3 Activation of Liver Macrophages in LIRI**

Constant monitoring for infection or non-infectious threats to tissue integrity is one of the major immune functions of liver-derived KCs (30). During hepatic injury, KCs can promote inflammasome formation while recognizing DAMPs or PAMPs that bind to PRRs such as NLRs. In the early stage of LIRI, ischemic injury leads to hypoxia in hepatocytes, which further causes pH changes and ATP depletion. These changes can increase the liver’s dependence on glycogen for energy production. At the same time, these events mentioned above promote the release of ROS, increase the intracellular calcium concentration, and exacerbate organelle damage, ultimately leading to cell damage or death.

Reperfusion after liver transplantation can enhance the inflammatory cascade, thereby aggravating liver injury. Furthermore, the destruction and death of hepatocytes and sinusoidal endothelial cells can trigger the release of DAMPs such as ATP and HMGB1. These DAMPs potentially activate hepatic macrophages such as KCs to awaken innate inflammatory responses, which may assemble the NLRP3

![Figure 2](https://example.com/image2.png)

**Figure 2** | The characterization of hepatic macrophages. The hepatic macrophages based on their origin and molecular features can be classified into liver-resident cells such as Kupffer cells (KCs) and liver capsular macrophages (LCMs), and non-resident cells such as monocyte-derived and peritoneal macrophages (PMs).
inflammasome and activate pyroptosis-regulated signaling pathways (31). These macrophages are critical in the mediation of LIRI, not only for recognizing damage-associated molecules to initiate inflammation and recruit immune cells, but also to help end inflammation and repair tissue damage.

The potential role of NLRP3 inflammasome activation pathway in LIRI has been investigated both in vitro and in vivo (32–34). Through the experiments, it was confirmed that the activation of NLRP3 inflammasome play a vital part in followed inflammatory response (33, 35). But utilizing the NLRP3 inflammasome inhibitors may mitigate hepatic inflammation through different signaling pathway.

Since both NLRP3 and caspase-1 knockdown attenuated the inflammatory response in the LIRI mouse model, and these two genes are upregulated during injury. Thus, it is thought that NLRP3 activation is critical for LIRI progression (32, 33). The knockdown of NLRP3 in model mice decreased the serum alanine aminotransferase levels, lowered the secretion of proinflammatory cytokines (such as IL-1β, IL-18, TNF-α, and IL-6) and inhibited the release of HMGB1. Overall, NLRP3 knockdown decreased the infiltration of inflammatory cells and protected the liver from I/R injury. Furthermore, depletion of myeloid cell-specific GSDMD suppressed warm LIRI, suggesting that macrophage and neutrophil pyroptosis have a driving role during hepatic ischemic stress (36). In the further study, some studies discovered that NLRP3 is highly expressed in macrophages and monocytes while downregulated in studies discovered that NLRP3 is highly expressed in mediating hepatocyte pyroptosis in the diabetic setting (41). Patients (40). Additionally, aggravated liver I/R injury was found in db/db mice with increased ROS expression. N-Acetyl-L-cysteine (NAC) treatment significantly inhibited hepatocyte NLRP3 inflammasome activation and pyroptosis in db/db mice after I/R, suggesting that ROS plays an important role in mediating hepatocyte pyroptosis in the diabetic setting (41).

Studies have shown that both exosomes and pyroptosis play a role in LIRI and are essential in neuronal death. In the LIRI rat model, the NLRP3 inflammasome is activated and caspase-1-dependent pyroptosis occurs in the hippocampus and cortex. Serum-derived exosomes from LIRI-challenged rats not only penetrated the blood-brain barrier (BBB) but also caused neuronal cell pyroptosis. Furthermore, in the exosome challenge group, ROS and malondialdehyde (MDA) production were increased, while the NLRP3 inhibitor (MCC950) attenuated LIRI-mediated pyroptosis of hippocampal and cortical neurons (42).

Robust activation of the NLRP3 inflammasome was demonstrated in KCs during LIRI (33). Huang et al. showed that during liver I/R, endogenous extracellular histones activate the NLRP3 inflammasome in KCs through TLR9-dependent production of ROS. Activation of the NLRP3 inflammasome can also regulate neutrophils and inflammatory monocytes infiltrating the liver after I/R. However, loss of NLRP3 provides a stable innate immune environment. Also, the numbers of DCs, neutrophils and inflammatory monocytes remained unchanged compared to liver I/R. Sham KO mice. These data suggest that depletion of the NLRP3 inflammasome downregulates the innate immune response by reducing the influx of innate immune cells in the ischemic lobe after liver I/R (33). Inhibition of the NLRP3 inflammasome also attenuates I/R-mediated hepatocyte injury and prevents several pro-inflammatory cytokines such as IL-1β, IL-18, HMGB1 and IL-6 by preventing the stimulation of caspase-1, and the release of NF-κB pathway. Inoue et al. found that NLRP3(-/-) neutrophils reduced the concentration of keratinocyte-derived chemokine-induced intracellular calcium, ROS activation, and actin assembly formation, resulting in impaired migratory activity. NLRP3 can regulate chemokine-mediated functions and neutrophil recruitment, leading to liver I/R injury independent of the inflammasome. These discoveries reveal a novel role for NLRP3 in the pathophysiology of LIRI (35).

Activation of NLRP3 in LIRI is regulated by various signaling pathway. The heat shock factor 1 (HSF1)-β-catenin axis mediates the activation of NLRP3 by regulating the X-box binding protein 1 (XBP1) signaling axis. HSF1 activation promotes β-catenin expression, which in turn inhibited XBP1, resulting in NLRP3 inactivation and LIRI mitigation (43). Recently, dexmedetomidine was reported to show therapeutic potential by repressing the activation of NLRP3 inflammasome and alleviating LIRI via the miR-494/JUND/P13K/AKT/Nrf2 axis (44).

Thioredoxin-interacting protein (TXNIP) is an oxidative sensor that in homeostasis and is released after ROS stimulation (45). TXNIP interacts with NLRP3 to promote its activation. Hypothermic oxygenated perfusion (HOPE) may modulate the TXNIP/NLRP3 inflammasome pathway from which liver injuries were reduced and liver function improved (46).

Autophagy, characterized by conserved autophagy, contributes to the degradation of intracellular components such as dysfunctional organelles, macromolecular complexes, long-lived cytoplasmic proteins, and foreign bodies. Recent studies have shown that autophagy negatively regulates the activation of the NLRP3 inflammasome during LIRI. Xue et al. reported that the antioxidant lycopene, elevated autophagosomes and increased protein levels of LC3B in KCs, and the autophagy inhibitor 3-methyladenine blocked the inhibitory effect of lycopene on the NLRP3 inflammasome in KCs (47). It is further demonstrated that lycopene promoted Nrf2/heme oxygenase 1 (HO-1) pathway activation and suppressed the NLRP3 inflammasome activation via enhancing KC autophagy (47). The expression of V-ATPase D2 subunit (ATP6V0D2) in liver macrophages was upregulated after LIRI which can promote the formation of autophagolysosomes to increase autophagy flux to limit the activation of liver inflammation.
Eva-1 homologous gene A (EVA1A) is a kind of lysosomal and endoplasmic reticulum-related protein that has been found to be involved in regulating autophagy and apoptosis (49). Knockdown of EVA1A in KCs inhibits the formation of autophagosomes through inhibiting formation of ATG5/ATG12 complex in I/R process. suppressed combined action with Atg16L1. Knockdown of transient receptor potential melastatin 2 (TRPM2) also prevents LIRI by inhibiting autophagy activation and NLRP3 inflammasome pathway, which is via the exogenous upregulation of LC3-II (50).

Abundant regulators inhibit NLRP3 inflammasomes activation to alleviate LIRI by regulating different pathways (51–62). Zarpou et al. found that Silibinin ameliorated inflammatory liver tissue injuries, including neutrophil and macrophage infiltration, hepatocyte degeneration, cytoplasmic vacuolation, vascular endothelial damages, and sinusoid dilation observed in the I/R group (51). Bruton’s tyrosine kinase (BTK) is mainly expressed on KCs and sinusoidal endothelial cells, and BTK inhibitor ibrutinib effectively attenuates liver I/R injury by suppressing activation of the NLRP3 inflammasome in KCs (52). T3 and fisetin suppressed I/R liver injury-dependent AMPK pathway (63, 64). While the 12-hours fasting exerted beneficial effects on the prevention of LIRI by increasing serum β-hydroxybutyric acid (BHB), thus up regulated forkhead box transcription factor O1 (FOXO1) and HO-1, and by reducing the inflammatory responses and apoptotic cell death via the down-regulation of NF-κB and NLRP3 inflammasome (65). SET domain-containing protein 8 (SET8) negatively regulates liver I/R-mediated inflammatory response and ameliorates LIRI by suppressing microtubule affinity-regulating kinase 4 (MARK4)/NLRP3 inflammasome pathway (66). Docosahexaenoic acid (DHA) ameliorated I/R-induced injury by inhibiting pyroptosis of hepatocytes induced in liver I/R injury in vivo and in vitro through the PI3K/Akt pathway, providing a potential therapeutic option to prevent LIRI (67). The histone deacetylase Siruin-1 (SIRT1) inhibits the downstream XBPI/NLRP3 inflammatory pathway by activating miR-182, thus alleviating LIRI in mice (Figure 3) (68).

Isoflurane preconditioning significantly relieved liver IRI in mice and LPS-induced inflammation in liver macrophages by reduced intracellular Ca $^{2+}$ levels, NF-κB translocation, and NLRP3 inflammasome activation in LPS-induced macrophages (69, 70). Isoflurane pretreatment also inhibited caspase-11 expression and noncanonical pyroptosis-related production of cytokines (IL-1β and IL-18). These findings suggest that isoflurane could be a pharmacological agent for liver IRI.
CONCLUSION

Recent advances continue to improve our understanding of the mechanisms involved in activation of NLRP3 inflammasome in LIRI. The KCs play a main part in the process. However, the pathological sequences of other macrophages such as recently identified LCM and other macrophages need to be further investigated. The advance in the subject also will improve the development of clinical strategies against LIRI and prevention of liver transplantation failure.

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AUTHOR CONTRIBUTIONS

TW: data analysis and writing. TS: statistics and data collection. CZ: statistics and program guidance. JC and DC: program guidance and supervision. All authors contributed to the article and approved the submitted version.

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