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Review Article

Emerging Roles of High-mobility Group Box-1 in Liver Disease

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Abstract

High-mobility group box-1 (HMGB1) is an architectural chromosomal protein with various roles depending on its cellular localization. Extracellular HMGB1 functions as a prototypical damage-associated molecular pattern that triggers inflammation and adaptive immune responses, mediated by specific cell surface receptors, including receptors for advanced glycation end products and toll-like receptors. Post-translational modifications of HMGB1 significantly impact various cellular processes that contribute to the pathogenesis of liver diseases. Recent studies have highlighted the close relationship between HMGB1 and the pathogenesis of acute liver injuries, including acetaminophen-induced liver injury, hepatic ischemia-reperfusion injury, and acute liver failure. In chronic liver diseases, HMGB1 plays a role in nonalcoholic fatty liver disease, alcohol-associated liver disease, liver fibrosis, and hepatocellular carcinoma. Targeting HMGB1 as a therapeutic approach, either by inhibiting its release or blocking its extracellular function, is a promising strategy for treating liver diseases. This review aimed to summarize the available evidence on HMGB1's role in liver disease, focusing on its multifaceted signaling pathways, impact on disease progression, and the translation of these findings into clinical interventions.

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Introduction

Acute liver injury (ALI) is a critical health concern with high morbidity and mortality, commonly triggered by bacterial endotoxin/lipopolysaccharide (LPS) and drug overdoses, such as acetaminophen (APAP).[1,2] Clinical treatment options for APAP-induced liver injury are currently limited, and the condition can rapidly progress to acute liver failure (ALF).[3] Nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) are primary contributors to the prevalence of chronic liver disease (CLD) in Western countries. The global incidence of these conditions has steadily increased in recent years, largely due to shifts in lifestyle and dietary patterns.[4,5] CLD can lead to critical complications, such as cirrhosis and hepatocellular carcinoma (HCC), which carry a poor prognosis in advanced stages. Consequently, identifying biological markers that facilitate early diagnosis of ALI and CLD is crucial.

High-mobility group box-1 (HMGB1), the most abundant non-histone nuclear protein, plays a major role in regulating DNA structure by binding to and bending DNA through the minor groove.[6] Recent studies have highlighted a notable increase in circulating serum HMGB1 levels in certain CLDs and ALI, indicating a close association between HMGB1 and these conditions.[7] Therefore, targeted interventions focused on HMGB1, such as inhibiting its synthesis and release or disrupting its signaling pathways through its receptors, hold promise for mitigating disease progression.[8] Moreover, emerging evidence suggests that HMGB1 is a mediator of liver diseases and a valuable biomarker for diagnosis and prognosis.[9–11] Compared to previous studies, this review provides a more comprehensive overview of the key types of HMGB1 post-translational modifications (PTMs) in liver disease, with a particular focus on the novel modification of lactylation. Furthermore, it updates recent findings on new molecular mechanisms and therapeutic targets associated with HMGB1 in various liver conditions, offering more cutting-edge insights. Thus, this review synthesizes current literature to elucidate the multifaceted roles and signaling pathways of HMGB1 in CLDs and ALI.

HMGB1

HMGB1 has multiple biological functions depending on its location. It is primarily translocated into the nucleus for architectural functions, including cell cycle regulation, cell death, and DNA replication/remodeling/repair.[12] Extracellular HMGB1 functions as a prototypical damage-associated molecular pattern (DAMP) that triggers inflammation and adaptive immune responses.[13] Receptors for advanced glycation end products (RAGE) and toll-like receptor (TLR) 4

Keywords: High-mobility group box-1; Liver disease; Damage-associated molecular pattern; Pathogenesis; Signaling pathway; Post-translational modifications.

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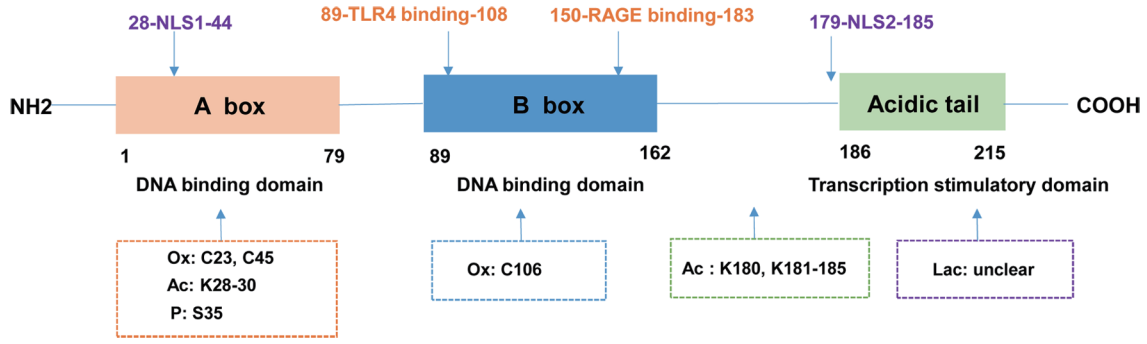

Fig. 1. Structure of HMGB1 protein. HMGB1 consists of three domains: two DNA-binding domains (A box and B box) and an acidic tail. The binding sites for TLR4 and RAGE on HMGB1 are specifically located at positions aa 89–108 and 150–183, respectively. NLSs serve as the primary sites for HMGB1 post-translational modifications. Cysteines can be oxidized at C23, C45, and C106. Lysines can undergo acetylation at K28-30, K180, and K181-185. A serine is subject to phosphorylation at S35. However, the specific modification sites for lactylation remain unclear. HMGB1, high-mobility group box-1; NLSs, nuclear localization signals; RAGE, receptor for advanced glycation end products; TLR, toll-like receptor; Ox, oxidation; P, phosphorylation; Ac, acetylation; Lac, lactylation.

are among the most prevalent and well-studied extracellular HMGB1 receptors.[14]

HMGB1 structure

HMGB1 expression is ubiquitous and conserved in higher eukaryotic species.[15] HMGB1 contains 215 residues organized into three domains: two DNA-binding regions [an A box (aa 9–79) and a B box (aa 95–163)], a C-terminus, and an N-terminus (Fig. 1).[16] The N-terminus of HMGB1 contains many positively charged lysine residues, while the C-terminus is rich in aspartate and glutamate.[17] The A box reportedly has anti-inflammatory activity, whereas the B box exhibits pro-inflammatory effects as a specialized antagonist. HMGB1's steady nuclear localization is mediated by two nuclear localization signals (NLSs), NLS1 (aa 28–44) and NLS2 (aa 179–185).[18] These NLSs contain specific sites for PTMs, such as oxidation (aa 23, aa 45, aa 105), acetylation (aa 28–30, aa 180, aa 181–185), and phosphorylation (aa 35), in liver disease. In subsequent sections, we will discuss extensively the impact of HMGB1 PTMs on its function and its crucial role in liver disease. Additionally, HMGB1 has two essential regions for receptor binding, aa 89–108 (TLR4) and aa 150–183 (RAGE).[19]

HMGB1 functions

HMGB1 performs various functions depending on its cellular localization. Within the nucleus, HMGB1 acts as a DNA chaperone, preserving chromosomal structure and function by maintaining nucleosome integrity, transcription, and DNA repair.[20] HMGB1 is passively released by necrotic cells or actively secreted by immune cells, making it a crucial mediator of inflammation, cell migration, and cell proliferation. Extracellular HMGB1 uniquely functions as a prototypical DAMP, acting as a standard alarm.[21] It triggers innate immune responses independently or through interaction with cytokines and other molecules by binding to various receptors.[22] Hence, HMGB1 is frequently implicated in various pathological conditions, including sepsis, arthritis, cancer, and neurodegenerative diseases. Additionally, HMGB1 has been involved in tissue regeneration. Extracellular HMGB1 can stimulate the proliferation and migration of stem cells, contributing to tissue repair and regeneration.[23,24] Moreover, HMGB1 plays a crucial role in regulating autophagy through various intracellular and extracellular signaling pathways.[25,26] A comprehensive understanding of HMGB1's multifaceted roles is essential, as dysregulation of its expression or function can cause pathological effects.

HMGB1 receptors

HMGB1 modulates inflammatory signaling cascades by binding to various receptors, including RAGE, TLR2/4/9, CXCL12/CXCR4, Mac-1, syndecan-1, and differentiation clusters.[27–29] We focus on RAGE and TLR4 due to their significance in liver disease.[30]

TLR4 is a key receptor involved in HMGB1 recognition and is released during liver injury and inflammation. It is expressed in various liver cells, including hepatocytes, Kupffer cells (KCs), endothelial cells, and hepatic stellate cells (HSCs).[31] TLR4 activation by extracellular HMGB1 initiates downstream signaling pathways, notably the nuclear factor-kappa B (NF-κB) pathway, which induces the production of pro-inflammatory cytokines and chemokines in hepatocytes.[32] This cascade amplifies the immune response in the liver and contributes to tissue damage and inflammation. The HMGB1/TLR4 signaling pathway has been implicated in the pathogenesis of various liver diseases, including NAFLD, ALD, viral hepatitis, and liver fibrosis.[33–35] The activation of this inflammatory signaling pathway is closely associated with liver disease progression. Therefore, targeting TLR4 and its associated signaling pathways in HMGB1-mediated liver disease has emerged as a promising therapeutic strategy.

RAGE is a transmembrane receptor belonging to the immunoglobulin superfamily. The interaction between HMGB1 and RAGE triggers signaling cascades that initiate inflammation, tissue regeneration, and immune responses.[36] Recent studies have provided valuable insights into the role of RAGE in liver disease.[37–39] It is expressed in hepatocytes, HSCs, liver sinusoidal endothelial cells (LSECs), KCs, and oval cells. Liver tissues collected from patients with ALD, NAFLD, and liver fibrosis exhibit elevated RAGE expression. Increased RAGE levels have been associated with the severity and progression of these diseases, suggesting a potential role for RAGE in liver pathology.[40,41] RAGE activation triggers downstream signaling cascades, including mitogen-activated protein kinases (MAPKs) and NF-κB pathways in hepatocytes,[42] promoting hepatic inflammation. HMGB1-RAGE interactions exacerbate immune cell recruitment to the liver, amplifying inflammatory responses. Additionally, the HMGB1-RAGE axis is crucial in liver fibrosis. The binding of RAGE to HMGB1 activates HSCs, which are vital effector cells in liver fibrosis. HSC activation induces the production of extracellular matrix proteins, causing fibrotic scar formation and tissue remodeling.[37] Inhibition of the HMGB1-RAGE axis has shown promise for attenuating liver fibrosis in experimental models. RAGE is a crucial receptor for HMGB1, which regulates HCC

Table 1. Functions and therapeutic strategies of HMGB1 PTMs in various liver disease

PTMs	Liver disease	Function	Therapeutic strategies
Acetylation	ALD ALF HIRI	Regulates the nucleus-cytoplasm shuttling of HMGB1	SIRT1 alleviates HMGB1 acetylation and translocation, ameliorating ALD[56] SphK1 inhibition diminishes HMGB1 intracellular translocation in ALF[57] Pachymic acid alleviates hepatic injury via SIRT1/HMGB1 signal pathway[58]
Phospho-rylation	ALD ALI Sepsis	Promotes HMGB1 secretion to cytoplasm	58-F or caspase-11/GsdmD inhibition protects against liver injury[59–61]
Oxidation	Liver fibrosis Hepatitis HCC	Induces translocation of HMGB1 from the nucleus to the cytoplasm	Nilotinib can improve liver fibrosis via RAGE/HMGB1 axis[62] HBx induces HMGB1 oxidation and NLRP3 activation, mediating liver inflammation[63] HMGB1 oxidation modulates the proliferation, migration, and metastasis abilities of tumor cells in HCC[64–67]
Lactylation	HIRI Sepsis	Increases HMGB1 cytoplasmic accumu-lation in hepatocytes or macrophages	HSPA12A reduces macrophage inflammation by inhibiting lactate production, decreasing HMGB1 lactylation and hepatocyte exosome secretion[55] Inhibiting intracellular lactate or blocking lactate signaling reduces HMGB1 lactylation, improving polymicrobial sepsis[68]

ALD, alcohol-associated liver disease; ALF, acute liver failure; HCC, hepatocellular carcinoma; HMGB1, high-mobility group box-1; HIRI, hepatic ischemia-reperfusion injury; HSPA12A, heat shock protein A12A; PTMs, post-translational modifications; SIRT1, sirtuin1; RAGE, receptor for advanced glycation end products; SphK1, sphingosine kinase 1.

proliferation and metastasis.[39] Conversely, modulation of the HMGB1-RAGE axis has been associated with enhanced liver regeneration and repair, emphasizing the dynamic role of this interaction in liver homeostasis.

PTMs of HMGB1 in liver disease

PTMs are crucial regulatory mechanisms for cellular proteins, serving various biological functions and modifying the charge state, hydrophobicity, conformation, and stability of proteins.[43,44] HMGB1, in particular, undergoes various PTMs.[45–51] Specific HMGB1 modifications significantly impact various cellular processes, including DNA stability, transcriptional regulation, protein localization, cell motility, and pro-inflammatory or pro-fibrogenic effects.[52–54] Moreover, several crucial HMGB1 PTMs, such as oxidation, phosphorylation, and acetylation, have been identified as contributors to the pathogenesis of liver diseases. Notably, lactylation has been investigated as a mediator of HMGB1 secretion from hepatocytes following hepatic ischemia-reperfusion injury (HIRI).[55] The following section focuses on the vital modifications involved in regulating liver diseases and the latest research advancements (Table 1).[55–68]

Acetylation of HMGB1 in liver disease

The acetylation of specific lysine residues in HMGB1 has been associated with its ability to modulate inflammatory responses, immune functions, and apoptosis.[69] Multiple lysine acetylation sites have been identified in NLS1 and NLS2. HMGB1 acetylation reportedly contributes to liver inflammation and injury in ALD by affecting its subcellular localization, DNA-binding activity, and interactions with other proteins.[70] HMGB1 acetylation has been shown to facilitate its translocation from the nucleus to the cytoplasm in cell and mouse models of alcohol-induced liver injury.[56] This pro-inflammatory effect was suppressed following treatment with resveratrol, a potent agonist of sirtuin 1 (SIRT1), by inhibiting HMGB1 acetylation and translocation. Moreover, HMGB1 acetylation is crucial in the pathogenesis of sepsis-associated liver injury. LPS induces HMGB1 expression in KCs and regulates its acetylation, influencing its intracellular translocation. Tian *et al*. found that sphingosine kinase 1 (SphK1) inhibition markedly improves sepsis-associated liver injury by inhibiting HMGB1 expression, intracellular translocation, and acetylation.[57] Additionally, HMGB1 acetylation exacerbates oxygen-glucose deprivation/reperfusion injury by promoting its translocation and release, leading to increased pro-inflammatory cytokine levels, oxidative stress, and hepatocellular apoptosis.[58]

Phosphorylation of HMGB1 in liver disease

The phosphorylation of serine residues within the NLSs of HMGB1 regulates its nucleocytoplasmic translocation, which is a critical step in its release into the extracellular space.[59] Zhao *et al*. found that HMGB1 phosphorylation promotes its release from the nucleus to the cytoplasm, mediating lipid degeneration in hepatocytes and facilitating the progression of ALD.[71] Calcium dysregulation during liver injury causes an elevated intracellular calcium load in hepatocytes.[72] The translocation and release of HMGB1 are reportedly regulated by the calcium/calcium-dependent kinase signaling pathway, which serves as an upstream signaling mechanism for HMGB1 phosphorylation. Activation of calcium-dependent kinases, such as PKCα and calmodulin-dependent protein kinase (CaMK) IV, promotes HMGB1 phosphorylation in H_2O_2-induced liver injury, facilitating its cytoplasmic translocation, subsequent release, and immuno-regulatory effect.[60] Similarly, Li *et al*. found that HMGB1 phosphorylation mediated by protein kinase C or calcium/CaMKII was associated with its release from hepatocytes in response to LPS stimulation.[61] However, the specific phosphorylation sites within HMGB1-NLS remain unclear.

Oxidation of HMGB1 in liver disease

HMGB1 oxidation primarily affects cysteine, lysine, and tyrosine residues, leading to their modification by reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide, and other oxidants, such as peroxynitrite.[48] HMGB1 oxidation can induce structural alterations that influence its protein-protein interactions, DNA-binding capac-

ity, and overall functionality in diverse biological processes. Investigations into HMGB1 oxidation have provided significant insights into its involvement in several diseases, such as liver fibrosis, HCC, and hepatitis. Oxidative stress is crucial in HSC activation during liver injury progression.[73] HMGB1 oxidation reportedly regulates liver fibrosis by activating HSCs and promoting collagen synthesis via RAGE/HMGB1/TGF-β and oxidative stress pathways.[62] Moreover, hepatitis B virus (HBV)-encoded X protein triggers HMGB1 oxidation and extracellular release in H_2O_2-stimulated HL7702 cells. The oxidized HMGB1 activates the NLRP3 inflammasome, inducing liver tissue inflammation and hepatocyte pyroptosis.[63] Thus, oxidized HMGB1 acts as a signaling molecule to regulate inflammatory reactions in HBV-infected tissues. Recent studies have shown that HMGB1 oxidation significantly influences HCC by modulating the proliferation and migration of tumor cells.[64] Notably, HMGB1-induced metastasis of tumor cells is considered an inflammatory response triggered by hypoxia stress through the RAGE/NF-κB and TLR4/caspase-1 signaling pathways.[75,66] Jing *et al*. proposed a novel mechanism by which HMGB1 oxidation promotes HCC proliferation and metastasis. HMGB1 upregulates the expression of the mitochondrial transport protein RHOT1 and tunneling nanotube-related protein RAC1 in hypoxic environments, promoting mitochondrial transfer and infiltration of tumor cells.[67] This novel mechanism provides a new perspective for exploring therapeutic strategies for HCC.

Lactylation of HMGB1 in liver disease

Lactylation is a novel epigenetic modification, heralding a new era for the comprehensive investigation of lactate metabolism.[74,75] Lactylation modifications alter protein structure and function, influencing protein folding, stability, and hydrophobicity. Consequently, they affect crucial biological processes, such as cellular signal transduction, cell cycle regulation, and metabolic control.[76] Multiple studies have demonstrated the essential contribution of protein lactylation in inflammation, cancer, and neuropsychiatric disorders.[77,78] Notably, lactylation modification is emerging as a crucial factor in liver disease and is closely associated with the development and progression of various conditions, such as NAFLD, fibrosis, and HCC.[79–81] Yang *et al*. revealed that macrophages can take up lactate through monocarboxylate transporters and facilitate HMGB1 lactylation via the p300/CBP pathway. Inhibiting intracellular lactate levels or blocking lactate signaling pathways can decrease the lactylation level of HMGB1 in exosomes, improving polymicrobial sepsis.[68] Furthermore, elevated levels of HMGB1 lactylation in hepatocytes during HIRI were closely associated with macrophage chemotaxis and inflammatory cytokine activation. However, hepatocyte heat shock protein A12A (HSPA12A) mitigates these effects by inhibiting lactate production from glycolysis, reducing HMGB1 lactylation and hepatocyte exosome secretion.[55] The Warburg effect is a crucial event in HCC development, where tumor tissues utilize the abundant lactate produced through aerobic glycolysis as a lactylation substrate.[82] The lactylation of histones and non-histones has garnered widespread attention, serving as a cornerstone of the tumor microenvironment (TME) and participating in HCC progression by regulating gene expression and cellular metabolism.[83–85] Unfortunately, there are currently no relevant publications on the involvement of HMGB1 in the pathogenesis of HCC. The author proposes that, influenced by the Warburg effect, HMGB1—functioning as a classic DAMP—could be a valuable target for elucidating the development and treatment of HCC through its lactylation modifications. Therefore, lactylation serves as a bridge between epigenetic and metabolic reprogramming in cancer cells. These findings suggest that HMGB1 lactylation is crucial in modulating inflammatory responses in liver diseases. However, studies on HMGB1 lactylation are currently limited to polymicrobial sepsis and HIRI. Interestingly, Gao *et al*. recently confirmed that mitochondrial pyruvate carrier 1 regulates fatty acid synthase lactylation at the K673 site and plays a role in treating NAFLD.[80] This is a valuable finding, providing a robust foundation for investigating the role of HMGB1 lactylation in NAFLD. Further in-depth investigations are urgently needed to explore the molecular mechanisms, including acetoacetyl coenzyme A-related writers and erasers, modification sites, and reaction kinetics, to develop new therapeutic interventions for liver disease.

HMGB1 in acute liver disease

HMGB1 in APAP-induced ALI

Acetaminophen-induced acute liver injury (AILI) has emerged as a significant public health concern, ranking among the top causes of drug-induced liver injury in developed nations.[86,87] APAP overdose triggers an inflammatory response and oxidative stress in hepatocytes at the onset of AILI. HMGB1, a DAMP associated with AILI, is passively released from necrotic hepatocytes, leading to elevated levels of HMGB1 in the systemic circulation.[88–90] Clinical studies have indicated that HMGB1 is a more sensitive biomarker than ALT in predicting the development of liver injury in patients with AILI. Additionally, it is vital in the stratification of early liver damage risk among AILI patients, enabling the customization of treatment strategies in clinical practice.[90] Pirnie *et al*. utilized high-resolution mass spectrometry to identify oxidized modifications of cysteine residues (Cys-23, Cys-45, and Cys-106) in HMGB1, further elucidating the HMGB1 phenotype secreted by hepatocytes in AILI. These findings identify HMGB1 as a potential early biomarker of liver toxicity following APAP overdose.[91]

HMGB1 enhances the immune response by activating macrophages and recruiting neutrophils during immune-mediated liver injury. This results in the release of excess cytotoxic ROS and proteases, exacerbating liver damage.[92] Extracellular HMGB1 binds to the RAGE receptor on the surface of neutrophils, selectively inducing their infiltration into necrotic sites, though it does not affect liver macrophage levels.[93] Additionally, HMGB1 can activate macrophages via the TLR4 signaling pathway, promoting the secretion of pro-inflammatory mediators, such as interleukin (IL)-23 and IL-17, which induce neutrophil migration and exacerbate liver damage.[94] HMGB1 also plays a crucial role in activating the macrophage NLRP3 inflammasome during AILI.[1] Activated NLRP3 inflammasomes mediate neutrophil infiltration and hepatocyte apoptosis by inducing Caspase-1 activation and upregulating IL-1β expression.[95] In the development of AILI, HMGB1 interacts with the TLR4 receptor and triggers macrophage activation through CD36, mediating Erk and Akt signaling and upregulating IL-1β and IL-6 expression. However, further investigation is needed to understand how HMGB1 mediates the function of CD36.[96] These studies substantiated the significance of HMGB1 in the innate immune modulation of AILI, facilitating crosstalk between hepatocytes and neutrophils. According to reports, extracellular HMGB1 can stimulate immune cells and trigger the necrosis of adjacent liver cells via the TLR4/TRIF/RIPK3 signaling pathway, accelerating liver cell necrosis.[97] Liu *et al*. proposed a mechanism in which APAP-induced activation of Caspase-1 in hepatocytes leads to neutrophil extracellular trap generation and subsequent release of pro-inflammatory cytokines. Notably, the depletion

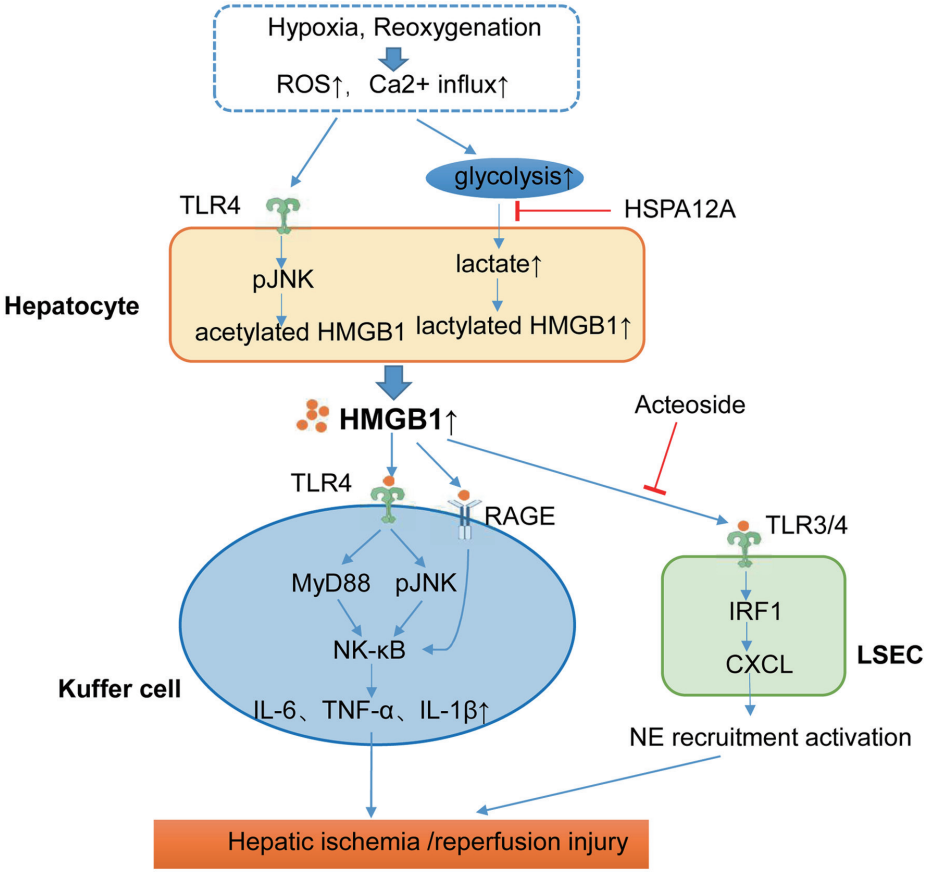

Fig. 2. The mechanism of HMGB1 release and its pathological impact in HIRI. HMGB1 lactylation promotes its extracellular translocation from the nucleus. HSPA12A can inhibit lactate production from glycolysis, thereby reducing HMGB1 lactylation and secretion. Extracellular HMGB1 binds to specific receptors on KCs, initiating an innate immune response. Moreover, HMGB1 specifically targets LSECs, leading to the nuclear translocation of IRF1 and CXCL1, which triggers neutrophil recruitment. ↑, increase; ↓, decrease; HMGB1, high-mobility group box-1; HIRI, hepatic ischemia-reperfusion injury; HSPA12A, heat shock protein A12A; pJNK, phosphorylation of c-Jun N-terminal kinase; LSECs, liver sinusoidal endothelial cells; NE, neutrophils; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TLR, toll-like receptor.

or inhibition of neutrophil extracellular traps in neutrophils reduces HMGB1 levels and prevents hepatocyte necrosis.[98]

N-acetylcysteine is currently the most effective treatment for APAP-induced liver damage; however, its therapeutic window is limited. Consequently, alternative therapies for treating AILI are required.[99] Treatment with a partially humanized anti-HMGB1 monoclonal antibody has shown higher efficacy and a broader therapeutic window in AILI compared to N-acetylcysteine.[100] Moreover, HMGB1-neutralizing antibodies have been shown to effectively decrease serum HMGB1 levels and bacterial translocation.[101] Additionally, sesamin exhibits a protective effect against AILI by mitigating hepatic oxidative stress and inflammatory responses through the inhibition of the HMGB1/TLR4/NF-κB signaling pathway, leading to decreased hepatocyte apoptosis levels.[102] Therefore, HMGB1 may serve as a pivotal therapeutic target for preventing APAP overdose-induced liver damage.

HMGB1 in HIRI

HIRI is a common complication of hepatic resection and liver transplantation.[103] The pathological progression of HIRI involves two interconnected phases: the onset of localized ischemia leading to hepatocyte injury, and the subsequent release of DAMPs, which triggers immune cell activation and initiates an inflammatory cascade that exacerbates liver damage.[104,105] HMGB1 serves as a crucial alarm molecule during the early stages of HIRI.[106] Numerous preclinical and clinical studies have confirmed that inhibiting HMGB1 release can effectively mitigate liver injury.[107,108] The release of serum HMGB1 after HIRI primarily depends on TLR4 activation.[109] TLR4 can specifically identify hepatocytes and induce HMGB1 release by activating the phosphorylation of the c-Jun N-terminal kinase and p38 signaling pathways. Therefore, hepatocytes are the primary contributors to the circulatory release of HMGB1 during HIRI.[110,111] Du *et al*. identified a novel regulatory mechanism for HMGB1 secretion by hepatocytes.[55] HMGB1 lactylation promotes its extracellular translocation from the nucleus, orchestrating macrophage chemotaxis and inflammatory activation. HSPA12A exerts strong hepatoprotective effects by inhibiting lactate production through glycolysis, reducing HMGB1 lactylation and secretion (Fig. 2). This study establishes a strong link between lactylation and HMGB1 secretion, highlighting its potential as a future therapeutic target for HIRI.

Notably, in early-stage HIRI, the activation of TLR4 on KCs triggers an innate immune response before neutrophil recruitment from the peripheral blood to the injured liver. The HMGB1/TLR4/NF-κB signaling pathway plays a critical role in the inflammatory cascade, leading to secondary immune injury following hepatic hypoxic.[112] Recent studies have fo-

cused on this signaling pathway and investigated the protective effects of various compounds, including drugs,[113,114] γ-oryzanol,[115] bioactive peptides (Ac2-26),[116] and TLR4 antagonists (eritoran),[117] which possess anti-inflammatory, antioxidant, and anti-apoptotic properties in HIRI. Additionally, RAGE is involved in HMGB1-mediated sterile inflammatory cascades.[118]

HMGB1 is a crucial mediator between hepatocytes and other liver cells, influencing the immune microenvironment and contributing to HIRI. LSECs play vital protective roles by maintaining vascular homeostasis, controlling inflammation, regulating vascular tone, and facilitating toxin clearance.[119] (Fig. 2) Upon recognition by TLR3/TLR4, extracellular HMGB1 specifically targets LSECs, leading to the nuclear translocation of IRF1 and subsequent transcription of CXCL1. This molecular cascade triggers neutrophil chemotaxis and accelerates the senescence-associated secretory phenotype in LSECs, further disrupting the liver sinusoid-like immune microenvironment. However, acteoside has shown protective effects against HIRI by targeting the HMGB1-TLR3/4-IRF1 signaling pathway and reversing LSEC senescence.[120] Tanemura *et al*. demonstrated that dabigatran enhances the expression of endogenous thrombomodulin in LSECs, reducing excessive serum HMGB1 levels, alleviating inflammation and cell apoptosis, preserving vascular integrity, and mitigating ischemia/reperfusion liver injury.[121]

HMGB1 in ALF

ALF is a prevalent and critical clinical condition stemming from various factors, including APAP toxicity, viral and autoimmune hepatitis, hepatic ischemia, drug-induced liver injury, and the use of herbal supplements. During the initial stage of ALF, the predominant pathogenic processes typically involve widespread hepatocyte necrosis and apoptosis within the liver tissue.[122] The release and activation of HMGB1 are crucial in the pro-inflammatory network that characterizes the pathophysiology of ALF.[123,124] Dynamic network analyses have revealed that serum HMGB1 expression is significantly higher than other inflammatory mediators in pediatric patients with ALF, suggesting that HMGB1 can serve as a critical predictive indicator for survival outcomes in affected children.[11] Furthermore, clinical cohort studies have confirmed that serum HMGB1 is an early and reliable biomarker for predicting acute kidney injury in patients with HBV-related acute-on-chronic liver failure, which is closely associated with poor prognosis.[125]

Hepatocyte death is recognized as a momentous event and a significant contributor to the progression of ALF. Notably, HMGB1 is significant in mediating various forms of cell death following immune imbalance in ALF.[126] For example, the tumor necrosis factor (TNF)-α/HMGB1 signaling pathway plays a pivotal role in triggering hepatocyte necroptosis in LPS/D-galactosamine-induced ALF. Treatment with TNF-α inhibitors (CC-5013) or glycyrrhizin can effectively inhibit HMGB1 release, ameliorating hepatocyte necroptosis and liver tissue damage.[127] Similarly, Wang *et al*. discovered that macrophages actively release extracellular vesicles (EVs) loaded with HMGB1, which selectively target hepatocytes. Through the HMGB1/RAGE signaling pathway, HMGB1 induces NLRP3 inflammasome activation, leading to hepatocyte necroptosis.[128] Furthermore, the levels of HMGB1-containing EVs are closely correlated with the degree of liver tissue injury. This highlights the significance of HMGB1-containing EVs as mediators of the communication between macrophages and hepatocytes, offering a promising strategy for targeted therapeutic interventions. Moreover, HMGB1 is crucial in mediating ferroptosis in ALF. The HMGB1 inhibitor glycyrrhizin has demonstrated a notable anti-ferroptotic effect in ALF by effectively decreasing Fe^{2+} and ROS levels while increasing glutathione levels in liver tissue.[129] However, the precise molecular mechanisms underlying HMGB1-mediated ferroptosis remain unclear and warrant further investigation.

Studies have shown that inhibiting HMGB1 activity or release can effectively mitigate the progression of ALF. The HMGB1-A box effectively suppresses the inflammatory activity of HMGB1 through competitive binding in LPS/D-Gal-induced ALF. The HMGB1-A box inhibits the TLR4/NF-κB signaling pathway, thereby reducing hepatocyte apoptosis and pro-inflammatory cytokine levels.[124] Additionally, the anti-inflammatory agent heparan sulfate selectively binds to HMGB1, targeting the HMGB1/RAGE axis and demonstrating effective hepatoprotective effects in APAP-induced ALF.[130] Furthermore, histone deacetyltransferase 4 (hereinafter referred to as HDAC4) is a vital regulator involved in the acetylation and nucleocytoplasmic shuttling of HMGB1. Tian *et al*. demonstrated that the SphK1/CaMKII-δ pathway serves as an upstream regulator of HDAC4 phosphorylation. Thus, SphK1 inhibition significantly reduces intracellular HMGB1 release, providing a potential approach for treating sepsis-related liver injury.[57]

HMGB1 in CLD

HMGB1 in NAFLD

The NAFLD incidence has risen significantly, transforming it into a global public health concern.[131] As the condition progresses, approximately 30% of patients with NAFLD develop an inflammatory state in the liver known as nonalcoholic steatohepatitis (NASH).[132] HMGB1 is an early mediator in the progression of NASH and is implicated in the pro-inflammatory microenvironment created by lipotoxicity.[33] Two clinical investigations were conducted to further investigate the potential role of HMGB1 as an early diagnostic biomarker of NAFLD. However, findings regarding the association between HMGB1 levels and the degree of liver fibrosis are inconclusive. One study reported a robust correlation between serum HMGB1 levels and liver fibrosis in pediatric patients with NAFLD.[7] Conversely, another study revealed no significant relationship between HMGB1 levels and liver inflammation in either pediatric or adult patients with NAFLD.[133] This discrepancy may be owing to the varied degrees of liver fibrosis among these patients. Additionally, no direct correlation between peripheral HMGB1 levels and the degree of liver tissue fibrosis has been established, highlighting the need for further research in this area. Sarcopenia is a severe condition common to various CLDs,[134,135] and timely identification and precise evaluation are essential. Recent studies have shown that sarcopenia is closely associated with NAFLD and serves as an independent risk factor for the progression of the disease.[136] Notably, studies have confirmed that HMGB1 plays a vital role in the pathogenesis of sarcopenia.[137,138] HMGB1 promotes skeletal muscle atrophy through an IL-18-dependent mechanism.[139] The elevation of IL-18 production induced by HMGB1 is mediated by the RAGE/p85/Akt/mTOR/c-Jun signaling pathway, indicating that the HMGB1/IL-18 pathway is a promising target for treating sarcopenia.

HMGB1 plays a dual role in the pathogenesis of NAFLD, potentially facilitating the progression of NASH or ameliorating hepatic lipotoxic injury, depending on its precise cellular localization. The upregulation of HMGB1 expression in hepatocytes is regulated by the JNK1/2-ATF2 axis and the miR-200 family in response to lipotoxic injury.[140] Extracellular HMGB1 initiates the TLR4/MyD88 signaling pathway in

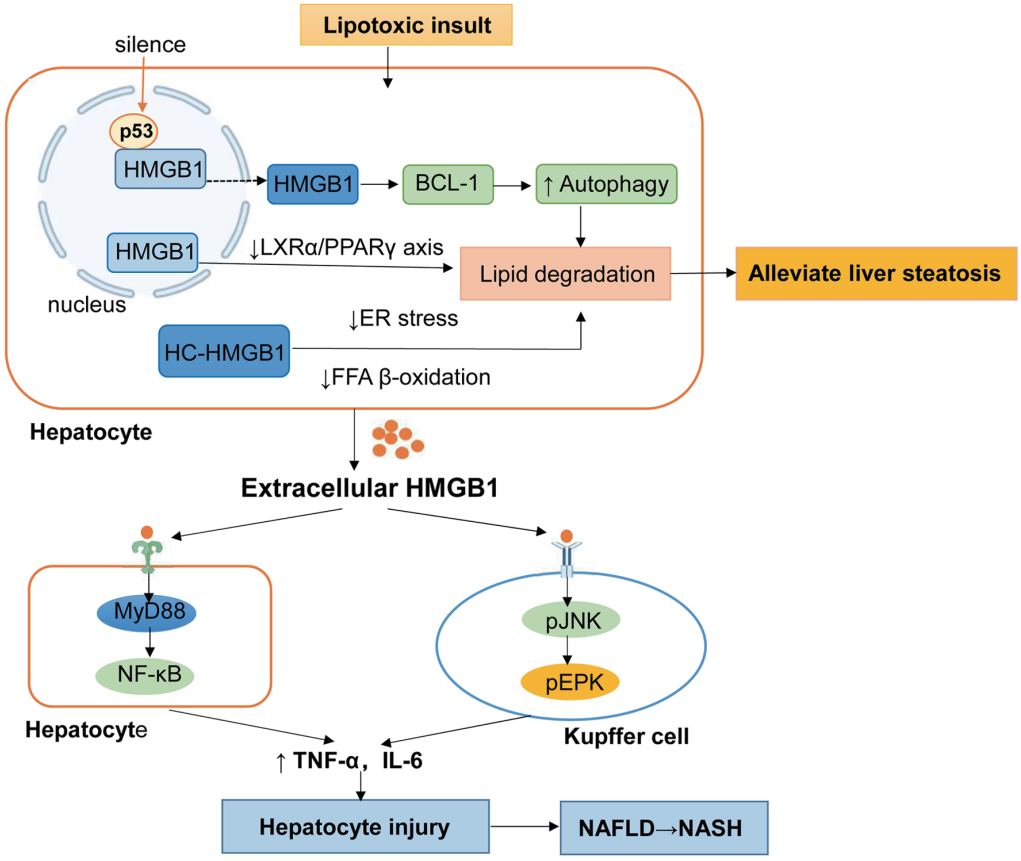

Fig. 3. Roles of nuclear and extracellular HMGB1 in the pathogenesis of NAFLD. Functional silencing of p53 promotes HMGB1 nucleocytoplasmic translocation. Then, HMGB1 triggers autophagy in hepatocytes by activating Beclin-1, facilitating lipid degradation. Nuclear HMGB1 also inhibits the LXRα/PPARγ axis, preventing liver steatosis. HC-HMGB1 can inhibit ER stress and prevent FFA β-oxidation. Conversely, extracellular HMGB1 stimulates the expression of TNF-α and IL-6 via the TLR4/MyD88 and RAGE/p-JNK/p-ERK signaling pathways. ↑, increase; ↓, decrease; BCL1, Beclin-1; ER, endoplasmic reticulum; FFA, free fatty acids; HMGB1, high-mobility group box-1; HC-HMGB1, hepatocyte-specific HMGB1; IL, interleukin; pJNK, phosphorylation of c-Jun N-terminal kinase; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RAGE, receptor for advanced glycation end products; TLR, toll-like receptor; TNF, tumor necrosis factor.

hepatocytes and induces an inflammatory response in the infusion of free fatty acids (FFA) or a high-fat diet.[33] (Fig. 3) Additionally, extracellular HMGB1 stimulates the expression of inflammatory mediators (TNF-α and IL-6) via the RAGE/p-JNK/p-ERK signaling axis, exacerbating hepatic inflammation and insulin resistance.[141] Therefore, extracellular HMGB1 serves as a DAMP and regulates innate immune signaling pathways, promoting the transition from NAFLD to NASH. Suppression of HMGB1 release from hepatocytes or treatment with HMGB1-neutralizing antibodies can mitigate liver damage.[142] Conversely, the intracellular function of HMGB1 in the development of NAFLD has emerged as a major focus of recent studies. Lin *et al*. demonstrated that hepatocyte-specific HMGB1 (HC-HMGB1) is crucial in maintaining endoplasmic reticulum (ER) homeostasis and preventing FFA-induced liver damage (Fig. 3). Compared with wild-type mice, HC-HMGB1-knockout (−/−) mice exhibited reduced expression of β-oxidation genes and increased ER stress markers in the liver, resulting in increased lipid accumulation and cell injury.[143] Nuclear HMGB1 is a potent inhibitor of liver lipogenesis. By specifically deleting the HMGB1 gene in hepatocytes, nuclear HMGB1 effectively inhibits the activities of the LXRα/PPARγ axis, preventing the development of liver steatosis (Fig. 3).[144] This finding suggests that HMGB1 might detach from chromatin in response to signals from the microenvironment, potentially influencing metabolic processes. Moreover, a novel HMGB1-mediated autophagy pathway has been reported to be involved in p53 regulation in NAFLD.[145] Functional silencing of p53 promotes the translocation of HMGB1 from the nucleus to the cytoplasm. Once in the cytoplasm, HMGB1 triggers autophagy in hepatocytes by activating Beclin-1, facilitating lipid degradation. Although the precise mechanisms by which hepatocellular HMGB1 regulates ER stress and lipid degradation remain unclear, these studies offer innovative insights into potential strategies for preventing the onset of NAFLD. These findings provide new insights for the clinical treatment of NAFLD, suggesting that HMGB1 acts as an alarming signal and plays a pivotal role in lipid metabolism.

HMGB1 in ALD

HMGB1 has been successfully implicated in ALD through various processes, including oxidative stress, mitochondrial dysfunction, inflammatory responses, disruption of lipid metabolism, and exposure to endotoxins, all of which are consequences of excessive alcohol consumption.[146] Clinical studies have confirmed that circulatory HMGB1 levels in patients with ALD are significantly elevated, serving as a biomarker to predict the clinical outcomes of alcoholic steatohepatitis.[10] As the disease progresses, liver tissue biopsies of patients with ALD show increased translocation of HMGB1 from the

nucleus to the cytoplasm.[147] The regulatory mechanisms of HMGB1 release are closely associated with PTMs, including acetylation, phosphorylation, and oxidative modifications. Further research revealed that genetic ablation of HMGB1 protects against alcoholic liver damage in mice, underscoring the deleterious impact of HMGB1 on the progression of ALD.[71] Moreover, HMGB1 plays a critical role in reducing ER stress in hepatocytes by promoting liver inflammation and apoptosis, which are crucial factors in the development of alcoholic steatohepatitis.[148] HSC activation is reportedly a major contributor to liver fibrosis. Previous studies demonstrated that HMGB1 is released from hepatic parenchymal cells upon ethanol exposure. This release promotes the migration of HSCs and LSECs to the site of liver injury, contributing to the development of liver fibrosis.[149] Xie *et al*. found that inhibiting autophagy could reverse alcohol-induced HSC activation and alleviate alcohol-induced liver injury in ALF mice.[150] They also identified the long non-coding RNA XIST as a competitive endogenous RNA for miR-29b, promoting HMGB1 cytoplasmic expression and inducing autophagy and HSC activation.[151]

Recent studies have investigated the effects of HMGB1 regulators or inhibitors on ALD. SIRT1 reportedly plays a crucial role in the negative regulation of HMGB1 in ALD. The administration of SIRT1 agonists has been shown to effectively suppress HMGB1 acetylation and release in hepatic tissue, thereby ameliorating liver injury associated with ALD.[56] BRD4 activates inflammatory responses in ALD via the BRD4/HMGB1 signaling pathway. Salvianolic acid A inhibits this pathway by reducing BRD4 expression and preventing HMGB1 release, showing promise for improving ethanol-induced hepatic inflammation, suggesting salvianolic acid A as a potential treatment for ALD.[152] Furthermore, digitoflavone can be used to treat ALD by inhibiting the HMGB1/TLR4 axis, reducing ethanol-induced inflammation, decreasing lipid production, and increasing lipid oxidation, thereby mitigating liver damage.[153] However, these findings are limited to animal studies, underscoring the need for clinical trials to evaluate the effectiveness and safety of HMGB1 inhibitors in patients with ALD and provide crucial empirical data for their clinical application.

HMGB1 in liver fibrosis

Liver fibrosis is a multifaceted pathological process significantly influenced by inflammation.[154] HMGB1 is a classical pro-inflammatory factor that plays a crucial role in HSC activation and extracellular matrix protein production.[155,156] HMGB1 expression in the liver is associated with the stage of fibrosis in individuals with hepatitis, primary biliary cirrhosis, and ALD.[38] Moreover, a prospective cohort study has demonstrated a potential correlation between elevated serum HMGB1 levels and decreased survival rates in patients with cirrhosis complicated by acute kidney injury.[157] Recent studies have focused on elucidating the specific mechanisms by which HMGB1 contributes to liver fibrosis. HMGB1 interacts with RAGE or TLR4 to activate a cascade of signaling pathways, including NF-κB/p65, MAPK, PI3K/Akt, and pMEK1/2/pERK1/2/pc-Jun. It also stimulates the activation and proliferation of HSCs, promoting the progression of fibrosis.[62,158,159] Additionally, HMGB1 can stimulate the generation of pro-inflammatory cytokines (such as IL-6, TNF-α, and IL-1), aggravating intrahepatic inflammation and accelerating fibrosis progression.[38,62,160,161]

IHMGB1 consists of two boxes: the B box, which promotes inflammation, and the A box, which inhibits TLR signaling and limits inflammatory responses.[162,163] Based on the unique structural attributes of HMGB1, studies have revealed a peptide derived from the A box that can reduce fibrotic lesions following liver injury. Furthermore, this HMGB1 peptide promotes macrophage polarization towards an anti-inflammatory profile, offering promising therapeutic benefits for treating liver fibrosis.[164] He *et al*. recently proposed an innovative pathogenic mechanism involving HMGB1 in the progression of HBV-induced liver fibrosis.[165] Their findings demonstrate that HMGB1 serves as a critical mediator of macrophage NLRP3 inflammasome activation. Additionally, epigallocatechin-3-gallate has been shown to promote the cytoplasmic autophagic degradation of HMGB1, reducing extracellular HMGB1 levels, inhibiting macrophage inflammatory complex activation, and improving liver tissue damage. However, the molecular mechanisms underlying how epigallocatechin-3-gallate inhibits macrophage NLRP3 activation remain unclear. Future studies should focus on identifying precise targets and methods to improve clinical interventions.

Another highly homologous protein, HMGB2, has been implicated in the pathogenesis of liver fibrosis and cirrhosis. Serum HMGB2 levels are significantly elevated in patients with liver fibrosis and cirrhosis. Genetic ablation of HMGB2 *in vivo* protects against CCl4-induced liver fibrosis owing to HSC inactivation, suggesting that HMGB2 could be a promising target for preventing the development of liver fibrosis.[166]

HMGB1 in HCC

The development of HCC is intricately associated with a process involving chronic cell death, inflammation, fibrosis, and repeated repair and regeneration responses.[167] HMGB1 is vital in the initiation and advancement of HCC. Multiple clinical studies have revealed that HMGB1 levels in the circulation and tumor tissues of patients with HCC are significantly elevated. Moreover, the increased presence of HMGB1 is strongly associated with tumor size, Edmondson grade, and tumor-node-metastasis staging, underscoring a direct association between elevated HMGB1 expression and unfavorable prognosis.[66,168,169] The role of HMGB1 in HCC is multifaceted and paradoxical owing to its distinct intracellular and extracellular localization.

HMGB1 promotes hepatocarcinogenesis: Liver-specific HMGB1 deficiency reduces HCC progression in CLD. Its deletion leads to reduced dendritic cells in tumors, suggesting a pivotal role in linking hepatocyte death to ductular reactions and hepatocarcinogenesis in CLD.[170] Athavale *et al*. reported that mice with impaired Hippo signaling pathways showed significant reductions in YAP activity, inflammation, fibrosis, and HCC burden after HMGB1 deletion. HMGB1-deficient mice displayed severe abnormalities in their intrahepatic bile ducts and developed hyperbilirubinemia. This implies that HMGB1 may contribute to the development of HCC and plays a role in maintaining the normal function of intrahepatic bile ducts under Hippo signaling deficiency.[171] Researchers recently proposed a regulatory role for HMGB1 in HBV-related early-stage HCC.[172] They suggested that elevated HMGB1 mRNA levels upregulate RICTOR mRNA expression by competitively binding to the miR-200 family. This HMGB1-mediated RNA-RNA crosstalk promotes glutamine metabolism in tumor cells, enhancing their stem-like properties and tumorigenesis via epigenetic modifications. Moreover, this crosstalk may affect the effectiveness of immunotherapy by increasing programmed death-ligand 1 (PD-L1) expression and PD-L1+ exosome activity. These findings provide new insights into potential targets for early-stage HCC treatment with anti-PD-L1 therapy. Cao *et al*. suggested that liver infection with H. hepaticus may influence the development of precancerous liver lesions primarily by promoting HMGB1 activation and accumulation.

HMGB1 promotes tumor proliferation and metastasis: RAGE is a key receptor for HMGB1, which regulates HCC proliferation and metastasis. The HMGB1/NF-κB signaling pathways, such as NF-κB/Ras-MAPK, NF-κB/STAT, and NF-κB/PI3K/Akt, are involved in modulating the expression of crucial signaling molecules and cytokines closely associated with cancer progression.[65,173–176] For example, HMGB1 stimulates increased KLF7 expression in tumor cells via the TLR4/RAGE-PI3K-AKT-NF-κB pathway. This causes the establishment of an HMGB1-KLF7-TLR4/PTK2 positive feedback loop, facilitating the development of HCC.[177] Autophagy significantly impacts the aggressive proliferation of tumors. A study revealed that HMGB1 serves as a crucial facilitator driving the advancement of HCC in autophagy-deficient livers.[170] HMGB1 is released through paracrine signaling and interacts with RAGE receptors on macrophages or ductal cells, stimulating the growth of liver tumors and modifying the TME.[178] In addition to conventional receptors, Pu *et al*. revealed that valosin-containing protein (VCP), a well-known molecule implicated in tumor metastasis and prognosis, significantly influences the advancement of HCC.[179] The interaction between the D1 domain of VCP and the A box of HMGB1 activates the PI3K/AKT/mTOR signaling pathway, enhancing the proliferation, migration, and invasion abilities of tumor cells. This demonstrates the pivotal involvement of HMGB1 in the VCP-driven progression of HCC, underscoring the potential of VCP and HMGB1 as promising therapeutic targets for HCC treatment.

HMGB1 regulates the TME: Alterations in the TME are pivotal in the advancement of HCC,[180] with HMGB1 serving a critical role in enhancing the production of inflammatory factors,[181] stimulating angiogenesis,[182,183] and facilitating immune evasion.[184,185] In hypoxic environments, HMGB1 expression is significantly increased in HCC, resulting in the infiltration of macrophages and their repolarization to promote IL-6 expression, which enhances the invasiveness and metastasis of tumor cells. Moreover, extracellular HMGB1 acts as a chemoattractant for leukocytes and a pro-inflammatory cytokine, prompting recruited leukocytes and resident immune cells to release TNF-α, IL-1, IL-6, and other cytokines.[181] Additionally, HMGB1 expression is increased by hepatitis B virus-encoded X protein activation, which plays a crucial role in the development of HBV-related liver cancer. HMGB1 modulates the IL-6/STAT3/miR-34a signaling pathway, facilitating epithelial-mesenchymal transition and tumor angiogenesis in HBV-related liver cancer. Therefore, HMGB1 may serve as a potential target for invasion and venous metastasis of HBV-related liver cancers.[182] Notably, mitochondrial transfer is a recently identified dynamic phenomenon associated with various human diseases, including cancer and cardiovascular diseases.[186] Jing *et al*. indicated that extracellular HMGB1 promotes mitochondrial transfer to influence the TME and the progression of HCC under hypoxic conditions.[67] HMGB1 enhances the expression of RHOT1 by boosting the activity of the NF-Y complex, regulating the recruitment of RAC1 to the cell membrane. This process facilitates mitochondrial transfer and promotes the migration and metastasis of tumor cells. Furthermore, elevated levels of HMGB1, RHOT1, and RAC1 in patients with HCC are associated with shorter overall survival. These findings demonstrate the complex interplay between hypoxia, HMGB1, and mitochondrial transfer during the progression of HCC, highlighting potential targets for therapeutic interventions.

Therapeutic potential of HMGB1

As discussed previously, HMGB1 is vital in the pathogenesis of acute and chronic liver diseases.[187] Specific strategies have been employed to target HMGB1 in treating these conditions, including inhibiting its release or impeding the function of extracellular HMGB1.[8,188]

HMGB1 antagonists effectively block excessive extracellular HMGB1 and alleviate inflammatory liver diseases.[189] An anti-HMGB1 monoclonal antibody reportedly protects animals against lethal sepsis-induced ALI by inhibiting HMGB1 endocytosis. These therapeutic approaches show promise for regulating HMGB1-mediated immune activation.[190] Furthermore, various chemical molecules and HMGB1-based peptides can bind directly to HMGB1 and inhibit its cytoplasmic translocation. Certain Chinese herbal medicines, such as curcumin, glycyrrhizin, and salvianic acid A, exhibit hepatoprotective effects by inhibiting the extracellular release of HMGB1 to alleviate liver inflammation.[152,158,191] Moreover, the HMGB1 peptide synthesized from the A box can drive macrophages toward an anti-inflammatory state, attenuating the advancement of liver fibrosis and showing promise as a therapeutic agent for cirrhosis.[164] Similarly, the peptide antagonist P5779 protects against experimental HIRI, APAP-induced liver toxicity, and sepsis lethality through the HMGB1/TLR4 signaling pathway.[192] Notably, HMGB1 is a crucial therapeutic target in HCC.[193] Multiple basic studies have shown that microRNAs (miR-320a, miR-325, miR-505, and miR-129-2) and long non-coding RNA (MIR22HG) are involved in the pathogenesis of HCC by negatively modulating the post-translational expression of HMGB1 in hepatocytes. This regulation suppresses tumor cell proliferation, invasion, and metastasis.[194–197]

Furthermore, some HMGB1 antagonists can effectively inhibit the transduction of inflammatory signaling pathways associated with HMGB1, thereby reducing its pro-inflammatory effects.[102] Digitoflavone has demonstrated potential in managing ALD by inhibiting the HMGB1-TLR4 signaling pathway.[153] In APAP-induced ALF, heparan sulfate exhibits a specific affinity for HMGB1, disrupting the HMGB1/RAGE axis and demonstrating notable hepatoprotective properties.[130] The protective effects of berberine-loaded nanostructured lipid carriers and aucubin against HIRI are achieved through the inhibition of the HMGB1/TLR4/NF-κB inflammatory signaling pathway, autophagy, and cell apoptosis.[113,198] A newly discovered RG-I pectin-like polysaccharide, YJ3A1, has shown potential in inactivating the HMGB1/TLR4/NF-κB and Akt signaling pathways, impeding the progression of NASH.[199] Wang *et al*. found that the intravenous administration of exosomes derived from adipose-derived mesenchymal stem cells could serve as a safe and effective cellular therapy targeting HMGB1 for HIRI treatment. This approach effectively suppresses the release of HMGB1 by obstructing the TLR4/MyD88/NF-κB/HMGB1 axis, mitigating hepatocyte apoptosis and pyroptosis in a miniature pig model of HIRI.[200]

HMGB1 is crucial in dampening inflammatory responses, safeguarding liver cells, and impeding the advancement of pathological processes by promoting excessive release and modulating receptor signaling pathways. Although there are challenges to its clinical application, ongoing studies on harnessing HMGB1 as a therapeutic target hold significant promise for effectively treating liver diseases.

Conclusions and future perspectives

Existing studies have confirmed that HMGB1 levels are significantly elevated in the serum of patients with various liver diseases, closely correlating with disease progression, the occurrence of complications, and clinical prognosis. These findings provide a crucial foundation for positioning HMGB1

as a diagnostic and therapeutic target in liver diseases. Furthermore, it is promising that many effective therapeutic drugs targeting HMGB1 in liver disease have been developed. A notable example is traditional Chinese medicine, including curcumin, glycyrrhizin, and salvianic acid A, which exhibit hepatoprotective effects by inhibiting the extracellular release of HMGB1. However, significant challenges remain in translating these findings into clinical interventions. On one hand, most of these clinical discoveries are based on retrospective studies from single centers, making it difficult to extrapolate the conclusions. Large-scale, multicenter prospective studies of HMGB1 in liver diseases are needed for validation. On the other hand, HMGB1 antagonists are still in the preclinical stage. Research on drugs targeting HMGB1 predominantly involves animal subjects, with a lack of studies involving human patient samples. Clinical trials are essential to assess the safety, tolerability, and efficacy of these drugs. Therefore, clinical practice guidelines should be updated, based on the effectiveness and safety of new therapies, to guide physicians in their treatment decisions.

HMGB1 plays a vital role in the pathogenesis of liver diseases; however, its molecular mechanisms of action remain unclear. Understanding the intricate relationship between HMGB1 and disease progression, treatment response, and clinical prognosis is particularly essential. Moreover, the differences in the signaling pathways involving HMGB1 in various hepatic cells, and how these pathways mediate crosstalk between cells, require further exploration. PTMs can modulate HMGB1 functions in liver pathophysiology, and targeting PTMs may offer new therapeutic strategies for the treatment of liver diseases. HMGB1 lactylation represents a highly valuable and challenging research direction. Notably, the specific molecular mechanisms of PTMs—including the writers and erasers, modification sites, and reaction kinetics—remain unclear. The precise signaling pathways and functions of HMGB1 lactylation in regulating the development of liver diseases require further study. Moreover, it remains to be determined whether other liver cells, apart from hepatocytes, can also undergo HMGB1 lactylation. Addressing these challenges will provide new insights into the pathogenesis and treatment of liver diseases.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization, data curation, writing (review & editing) and methodology: LW; conceptualization, writing (original draft preparation), software and formal analysis: ZD; conceptualization, writing (original draft preparation) and literature review: YZ; conceptualization, supervision, visualization, writing (review & editing) and funding acquisition: LP. All authors have read and agreed to the published version of the manuscript.

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