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REVIEW ARTICLE

DAMPs and sterile inflammation in drug hepatotoxicity

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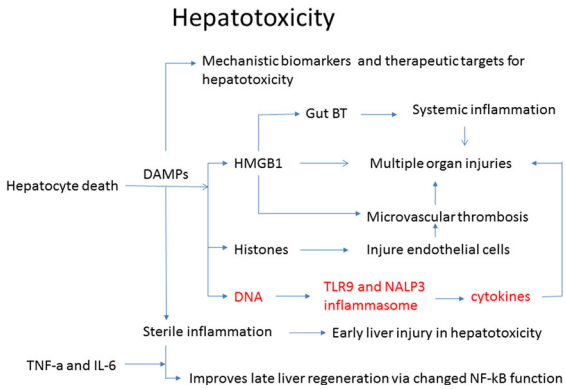
Abstract

Drug hepatotoxicity is the leading cause of acute liver failure (ALF) in the developed countries. The early diagnosis and treatment are still problematic, and one important reason is the lack of reliable mechanistic biomarkers and therapeutic targets; therefore, searching for new biomarkers and therapeutic targets is urgent. Drug hepatotoxicity induces severe liver cells damage and death. Dead and damaged cells release endogenous damage-associated molecular patterns (DAMPs). Increased circulating levels of DAMPs (HMGB1, histones and DNA) can reflect the severity of drug hepatotoxicity. Elevated plasma HMGB1 concentrations can serve as early and sensitive mechanistic biomarker for clinical acetaminophen hepatotoxicity. DAMPS significantly contribute to liver injury and inhibiting the release of DAMPs ameliorates experimental hepatotoxicity. In addition, HMGB1 mediates 80% of gut bacterial translocation (BT) during acetaminophen toxicity. Gut BT triggers systemic inflammation, leading to multiple organ injury and mortality. Moreover, DAMPs can trigger and extend sterile inflammation, which contributes to early phase liver injury but improves liver regeneration at the late phase of acetaminophen overdose, because anti-inflammatory treatment reduces liver injury at early phase but impairs liver regeneration at late phase of acetaminophen toxicity, whereas pro-inflammatory therapy improves late phase liver regeneration. DAMPs are promising mechanistic biomarkers and could also be the potential therapeutic targets for drug hepatotoxicity. DAMPs-triggered sterile inflammation contributes to liver injury at early phase but improves liver regeneration at later phase of acetaminophen hepatotoxicity; therefore, anti-inflammatory therapy would be beneficial at early phase but should be avoided at the late phase of acetaminophen overdose.

Graphical abstract



Keywords Hepatotoxicity · DAMPs · Sterile inflammation · Regeneration

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Abbreviations

ALF	Acute liver failure
MOF	Multiple organ failure
SIRS	Systemic inflammatory response syndrome
BT	Bacterial translocation
HMGB1	High mobility group box 1
NETs	Neutrophil extracellular traps
DAMP	Damage-associated molecular pattern
TLR	Toll-like receptor
APAP	Acetaminophen
MODS	Multiple organ dysfunction syndrome
LPS	Lipopolysaccharide

Introduction

Drug hepatotoxicity is the main cause of acute liver failure (ALF) in the west industrialized countries [1]. Acetaminophen hepatotoxicity is a global issue; it is responsible for nearly half of the ALF cases in the US and remains the leading cause of liver transplantation [1]. Drug hepatotoxicity induces severe liver cells damage and results in hepatocyte cell death and inflammation [2, 3]. Dead, dying and damaged cells release DAMPs [4, 5], leading to increased circulating DAMPs concentrations in drug-induced acute fatal liver injury [5]. Once rapidly released extracellularly, these DAMPs can activate the innate and adaptive immune system [6] and resultantly initiate and extend sterile inflammation [4], which also significantly contribute to hepatotoxicity [5]. Therefore, endogenous DAMPs, also known as alarmins, can signal cellular damage [6]. Elevated circulating levels of DAMPs in patients and animals with severe acute pancreatitis (SAP) positively correlate with disease severity [4]. Inhibiting DAMPs (for example, HMGB1, histones and DNA) release can significantly ameliorate experimental SAP and multiple organ injuries [4]. Similarly, the increased plasma DAMPs concentrations can accurately reflect the severity of liver injury and blockade of these alarmins can attenuate experimental drug hepatotoxicity [5]. These evidences indicate that DAMPs could be the promising mechanistic biomarkers and the potential therapeutic targets for drug hepatotoxicity. Currently, the early diagnosis of drug hepatotoxicity and the treatment are still problematic, one important reason is lack of reliable biomarkers and therapeutic targets. Anti-inflammatory therapy is clinically available; however, when and how to use the anti-inflammation treatment is still difficult in practice, because it is increasingly clear that inflammation contributes to liver injury at early phase but improves hepatocyte regeneration at the late phase of drug hepatotoxicity. In this manuscript, we review the current understanding of DAMPs and DAMPs-initiated sterile inflammation in drug hepatotoxicity.

HMGB1 in drug hepatotoxicity

HMGB1 is a non-histone nuclear protein that binds DNA [7]. Under resting conditions, HMGB1 is localized in the nucleus, where HMGB1 is involved in chromosomal DNA repair and contributes to nucleosome mobility by promoting histone sliding along the DNA strand [7]. Intracellular HMGB1 also plays an important role in modulating gene expression [7]. Following cell activation, HMGB1 undergoes post-translational modifications (such as acetylation) and the modified HMGB1 can translocate to cytoplasm. Extracellularly HMGB1 acts as DAMPs to interact with receptors that include RAGE (receptor for advanced glycation endproducts) as well as TLR2 and TLR4; therefore, extracellular HMGB1 can activate the innate immune system and mediate a wide range of pathological responses including sterile inflammation [7]. Among the DAMPs molecules, HMGB1 is a typical alarmin [5, 7] and plays an important role in the pathogenesis of drug hepatotoxicity [5].

HMGB1 is a critical mediator of lethal systemic inflammation

Drug hepatotoxicity is featured with severe liver cell damage and death [2]. Dead and damaged cells can rapidly release HMGB1 [8–10], which can also be actively secreted by immunocompetent cells [10]. Extracellular HMGB1 can signal inflammation [9] and modulate inflammatory cascade [11, 12] in which HMGB1 can stimulate LPS-stimulated macrophages to secrete early inflammatory cytokines TNF-α and IL-6 [11, 12]. HMGB1 is a potent late inflammatory mediator [8]; this well-studied alarmin molecule plays a critical role in lethal systemic inflammation [13, 14] in which HMGB1 may damage vascular endothelial cells and cause microvascular thrombosis, and this detrimental effect can lead to multiple organ dysfunction [15]. In addition, HMGB1 has a longer therapeutic window as compared to those early inflammatory cytokines: serum TNF-a and IL-6 are elevated for 5 days after the onset of sepsis, whereas circulating HMGB1 levels are increased for at least 3 weeks [16]. Therefore, compared to early inflammatory cytokines, HMGB1 is potentially a better therapeutic target for treating drug hepatotoxicity and sepsis, because drug-induced acute fatal liver injury has a potential to develop sepsis [5, 17, 18].

Circulating HMGB1 level is increased in drug hepatotoxicity

The clinical presentation of acetaminophen hepatotoxicity may vary; this makes the early diagnosis more difficult. Therefore, it is necessary to find new mechanistic biomarkers. Since HMGB1 can be rapidly released by damaged/dead hepatocyte and extracellular HMGB1 can signal cellular damage [6], HMGB1 might be a good biomarker candidate for the early diagnosis of drug-induced liver injury, and this notion is supported by the following evidences. In multiple acetaminophen-induced hepatotoxicity animal models, the significantly elevated circulating HMGB1 concentrations can signal liver cells injury [6] and reflect the severity of drug hepatotoxicity [17, 18]. In an acetaminophen-induced hepatotoxicity clinical trial, the circulating HMGB1 concentration represents hepatocyte necrosis, and serum hyper-acetylated HMGB1 levels indicate pyroptosis and immune cell activation [19, 20]. The increased plasma HMGB1 levels are able to sensitively reveal early acetaminophen-induced acute liver injury at first presentation to hospital [19]. In addition, the markedly increased total and acetylated HMGB1 concentrations indicate worse prognosis in the same acetaminophen clinical trial [20]. Moreover, ALF patients also have high levels of circulating HMGB1, which are positively correlated with disease severity [21, 22]. These data indicate that HMGB1 is a promising mechanistic biomarker of clinical drug hepatotoxicity (Fig. 1).

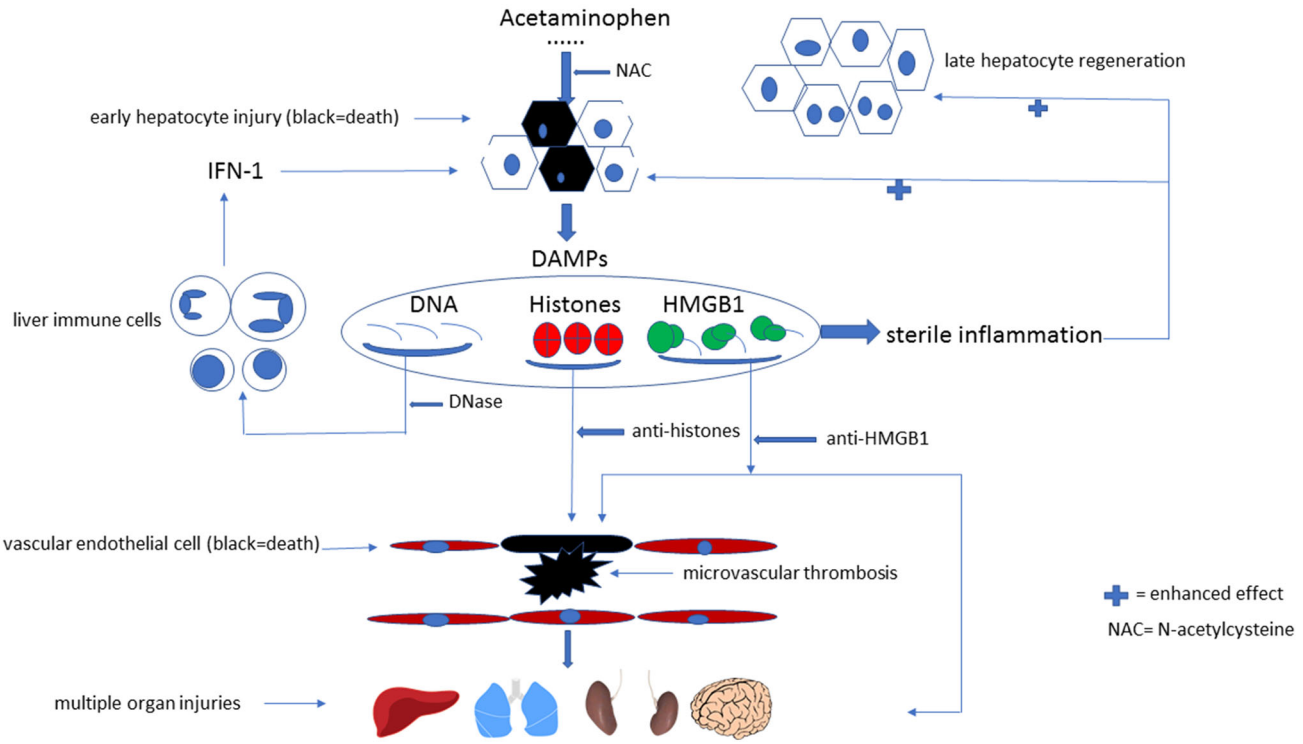
HMGB1 significantly contributes to drug hepatotoxicity and other vital organ injuries

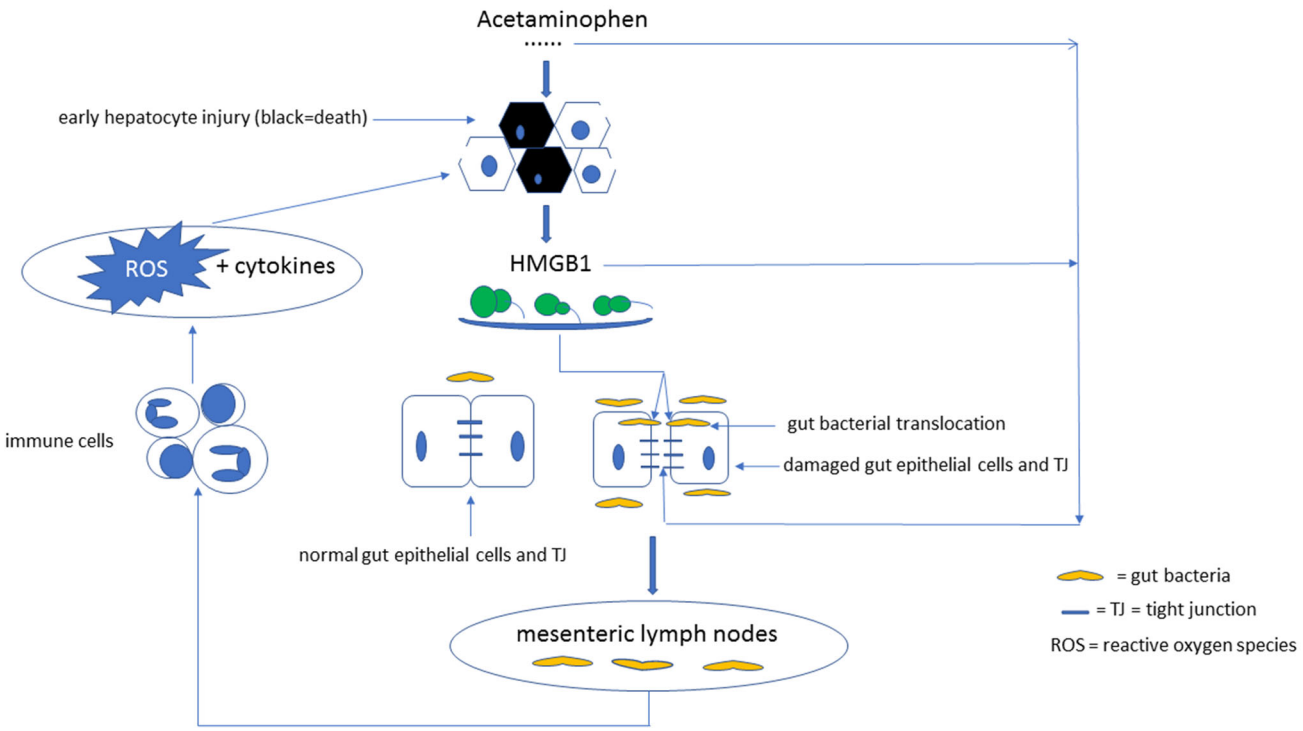
Exogenous HMGB1 injection to mice can induce liver injury in which the serum ALT level is even higher than alcoholic steatohepatitis [23]. In a lethal acetaminophen overdose animal model, HMGB1 markedly impairs hepatocyte regeneration and blockade of HMGB1 significantly improves the late phase liver structure recovery [17]. Neutralization of HMGB1 can also ameliorate the early phase liver injury in two different experimental hepatotoxicity models, which are induced by acetaminophen overdose and D-galactosamine/LPS [24, 25]. In addition, inhibition of HMGB1 cytoplasmic translocation in liver cells can reduce acute fatal liver injury induced by D-galactosamine/LPS [26]. These data indicate that HMGB1 significantly contributes to drug hepatotoxicity at both the early injury phase and the late regeneration phase.

Moreover, circulating HMGB1 concentration has been reported as a sensitive disease biomarker [27], which can be used to reliably predict the severity of severe acute pancreatitis (SAP) in clinic [28, 29]. The elevated levels of circulating HMGB1 can accurately reflect organ dysfunction, infection and fatality in patients with SAP [28, 29]. Inhibition of HMGB1 release can reduce pancreatic injury in an animal model of SAP [30]. HMGB1 has also been proved to promote acute kidney injury in multiple animal models, which are induced by renal ischemia–reperfusion [31], sepsis [32] and SAP [33]; inhibition of HMGB1 can attenuate kidney injury in these animal models. HMGB1 also significantly contributes to acute lung injury (ALI) in multiple animal models, which are induced by hemorrhagic shock [34], hyperoxia [35] and SAP [36]; blockade of HMGB1 protects against lung injury in these models.

HMGB1 mediates gut BT that triggers systemic inflammation during acetaminophen hepatotoxicity

Gut mucosal injury and BT play an important role in the development of multiple organ dysfunction during drug-induced hepatotoxicity, because acetaminophen overdose can induce evident mucosal injury [18], which can facilitate the leakage of gut luminal bacteria/LPS into the systemic circulation to trigger systemic inflammatory response syndrome (SIRS) [37]. The latter can lead to multiple organ dysfunctions (MOD), which can culminate in multiple organ failure (MOF) and fatality [38]. Therefore, the digestive tract is considered as the origin of systemic inflammation [38]. The following evidences support the notion that HMGB1 plays an important role in gut BT in drug hepatotoxicity. Exogenous HMGB1 injection to mice can induce gut mucosal injury and evident intestinal BT [23]. In an acetaminophen-induced hepatotoxicity murine model and a severe acute pancreatitis animal model, serum HMGB1 levels are elevated and the circulating HMGB1 levels are correlated with the amount of gut BT [17, 18, 39]; neutralization of HMGB1 decreases 70–80% of gut BT in both models; however, gut mucosal injury is not significantly improved in these two models [18, 39]. These data indicate that gut bacteria need adhere to the damaged gut mucosa to cross the intestinal mucosal barrier; however, this step is necessary but insufficient to complete the complicated gut BT procedure [18, 39]; HMGB1 is one of the important factors that are also needed to mediate intestinal BT; gut bacteria cross the mucosal barrier likely via an active "transcellular" pathway instead of a passive "paracellular" pathway through the damaged tight junction between the mucosal epithelial cells. It is becoming increasingly clear that gut BT can induce systemic inflammation in critical illness such as severe acute pancreatitis and trauma [40, 41]. Systemic inflammation can lead to MOD and mortality [42]. Therefore, HMGB1


Acetaminophen
NAC
late hepatocyte regeneration
early hepatocyte injury (black=death)
IFN-1
DAMPs
liver immune cells
DNA
Histones
HMGB1
sterile inflammation
DNase
anti-histones
anti-HMGB1
vascular endothelial cell (black=death)
microvascular thrombosis
multiple organ injuries
= enhanced effect
NAC= N-acetylcysteine


Acetaminophen
early hepatocyte injury (black=death)
ROS
+ cytokines
HMGB1
immune cells
gut bacterial translocation
damaged gut epithelial cells and TJ
normal gut epithelial cells and TJ
mesenteric lymph nodes
= gut bacteria
= TJ = tight junction
ROS = reactive oxygen species

◀**Fig. 1** In drug hepatotoxicity, the dying and dead hepatocyte releases damage-associated molecular patterns (DAMPs) such as HMGB1 and histones. HMGB1 significantly contributes to acetaminophen-induced hepatotoxicity and mediates gut bacterial translocation (BT), which induces systemic inflammation, leading to multiple organ dysfunction. Extracellular histones damage vascular endothelial cells and activate platelets to induce vascular thrombosis; this detrimental effect can lead to acute liver, lung, kidney and brain injuries. DNA released from dying hepatocytes is capable of activating liver immune cells via TLR9 and NALP3 inflammasome complexes resulting in cytokine production; the latter can amplify liver injury. Therefore, HMGB1, extracellular histones and DNA can signal cellular injury and are promising mechanistic biomarkers, and these molecules could also be the potential therapeutic targets for drug hepatotoxicity. In addition, DAMPs trigger sterile inflammation; the latter contributes to liver injury at early time point but improves liver regeneration at the late phase of drug hepatotoxicity. Pro-regenerative cytokines TNF-a and IL-6 can prime the quiescent hepatocyte to facilitate liver regeneration at the late time point of drug hepatotoxicity

appears to be the important factor that links BT and systemic inflammation in drug hepatotoxicity.

Extracellular histones in hepatotoxicity

Histones are important nuclear proteins that facilitate packaging of DNA into nucleosomes [43]. Upon cell injury or cell signaling process, histones can be passively or actively released [43–45]. Extracellular histones act as DAMPs to interact with receptors that include TLR2 as well as TLR4 to induce sterile inflammatory organ injury [43–45].

Circulating histones concentrations are increased in patients and animals with hepatotoxicity

The necrotic/damaged liver cells can passively release histones during drug hepatotoxicity, leading to elevated levels of circulating histones [44, 45]. The increased circulating histones levels can accurately reveal the severity of hepatotoxicity in two different animal models, which are induced by lethal doses of concanavalin A and acetaminophen [45]. Except the animal models, patients with acute-on-chronic liver failure and ALF are also reported to have elevated circulating histones concentrations, which can reflect disease severity and fatality [46, 47].

Extracellular histones significantly contribute to hepatotoxicity

Extracellular histones are cell toxic to host cells; therefore, the noxious extracellular histones can promote drug-induced liver injury by damaging tissue cells and killing endothelial cells [43, 45]. In addition, extracellular histones can also elicit immuno-stimulatory effect to exaggerate multiple organ injuries [43–45, 48, 49]. In the following two different animal models, lethal doses of concanavalin A and acetaminophen are used to induce hepatotoxicity, and blockade of histones can attenuate acute fatal liver injury in both animal models, suggesting that extracellular histones are the major mediators of death in acute fatal liver injury [45]. In another animal model, the acute liver failure is induced by D-galactosamine/LPS, circulating histones can exacerbate systemic inflammation and neutralization of histones can ameliorate the acute liver failure in this model [50]. Except animal models, ALF patients also have increased serum histones levels, which can induce hepatocyte death and stimulate monocytes to release inflammatory mediators; these detrimental effects can be reversed by heparin treatment that can bind histones, suggesting that circulating histones are crucial mediators of systemic inflammation in ALF patients [46]. Histone H4 together with increased circulating NETs can activate platelets to facilitate the formation of microvascular thrombosis in sepsis [39, 45, 49, 51]. Extracellular histones can damage microvascular endothelial cells and induce the formation of microvascular thrombosis, these detrimental effects can lead to acute kidney [51, 52], lung [53] and brain injury in multiple animal models, and neutralization of histones can ameliorate these organ injuries and reduce the brain infarct size [54]. These data suggest that histones could be the potential novel biomarkers and therapeutic targets in drug-induced acute fatal liver injury.

Extracellular DNA contributes to acetaminophen-induced liver injury

After a drug overdose, hepatocytes may rupture and release a large amount of DNA, this can lead to the increased levels of circulating DNA [44, 45]. ALF patients also have increased plasma DNA levels that are closely associated with extracellular histones [44]. As part of the DAMPs, DNA together with histones/HMGB1 can stimulate the formation of neutrophil extracellular traps (NETs), and NETs can augment liver injury induced by sterile inflammation [48]. In addition, DNA together with histones/HMGB1 can mediate sterile inflammatory liver injury during drug hepatotoxicity, and DNase treatment can attenuate liver injury by reducing DNA levels [48]. Moreover, necrosis-derived DNA can stimulate liver immune cells (such as sinusoidal endothelial cells) via TLR9 and NALP3 inflammasome to release cytokines (such as IFN-1); the latter can amplify acetaminophen-induced liver necrosis [55, 56].

Inflammation contributes to liver injury at early phase but improves liver regeneration at late phase of acetaminophen hepatotoxicity

Drug hepatotoxicity results in cell death and sterile inflammation, and the latter also contributes to drug-induced liver injury [2].

Early inflammatory cytokines in drug hepatotoxicity

Early inflammatory mediators such as TNF-a, IL-6 and IL-1 β contribute to early phase acetaminophen hepatotoxicity via NF-kB signal pathway [57, 58], and these detrimental effects can be reduced by anti-inflammatory therapies at the early phase of acetaminophen overdose [57, 58]. TNF-a acts synergistically with HMGB1 to promote the acute fatal liver injury induced by D-galactosamine/LPS, and blockade of TNF-a and HMGB1 can synergistically ameliorate liver injury [59]. These data indicate that early inflammatory mediators promote liver injury at the early phase of drug hepatotoxicity.

TNF-α is a well-known early pro-inflammatory mediator that promotes hepatic tissue damage at the early phase of acetaminophen overdose [57–59]. However, TNF-α has also been reported as an important pro-regenerative cytokine that can facilitate the late phase liver regeneration during acetaminophen toxicity, because TNF-a can make the quiescent hepatocyte become more responsive to growth factors [60–62]. Acetaminophen overdose induces hepatocyte necrosis; liver regeneration is, therefore, vital for survival after the drug overdose insult [60, 63]. Prior to liver repair, the pro-regenerative cytokines such as TNF-α, IL-6 and IL-8 are needed to sensitize the hepatocyte, this process is crucial for the late phase liver regeneration [60, 64, 65], and this notion is supported by the following evidences. In an acetaminophen-induced acute liver injury animal model, Ringer's lactate solution (RLS) is used to improve the late phase hepatocyte regeneration, because this frequently used resuscitative fluid has pro-inflammatory effect, which can elevate the circulating levels of IL-6, IL-8 [66, 67] and TNF-α in patients and animals [67, 68]. As compared to the saline treatment, RLS therapy increases hepatic tissue TNF-α level at the early phase and improves liver repair at the late phase of acetaminophen hepatotoxicity; the improved liver regeneration is associated with elevated serum TNF-α concentration [69]. In another acetaminophen overdose animal model, the human well-tolerated novel anti-inflammatory agent ethyl pyruvate (EP) is used to ameliorate liver injury. Compared to the saline therapy, EP treatment attenuates liver injury at early phase but impairs hepatocyte regeneration at the late phase of acetaminophen overdose, and the impaired late phase liver repair is associated with decreased serum TNF-α level [70]. In addition, neutralization of HMGB1 enhances hepatocyte regeneration at the late phase of acetaminophen overdose, and this beneficial effect is associated with increased hepatic TNF-α level [17]. These data indicate that TNF-α might contribute to early liver injury, which possibly acts synergistically with the other early inflammatory mediators. However, increased TNF-α level at early phase might prime hepatocyte and facilitate the late phase liver regeneration in acetaminophen hepatotoxicity.

Kupffer cells in acetaminophen hepatotoxicity

Kupffer cells (KCs) are hepatic resident phagocytes that serve as sentinels for liver homeostasis [71]. Once activated, KCs can release a large amount of inflammatory mediators that can promote liver injury [69]. Therefore, KCs play an important role in acetaminophen hepatotoxicity [72, 73]. In an acetaminophen overdose animal model, the depletion of KCs protects against liver injury at the early time point [73] but leads to more severe liver injury at the late phase of hepatotoxicity [72]. Macrophages contain two different subsets [74]. The M1 macrophages appear to promote liver injury at the early time point but the M2 macrophages show evidence to protect against liver injury at the late time point of acetaminophen overdose [74]. Except that KCs can produce inflammatory cytokines, new evidence shows that KCs also express multiple angiogenic factors, which can induce liver sinusoidal endothelial cell (LSEC) proliferation and migration [75]. When KCs are depleted in acetaminophen-induced liver injury animal models, this can significantly affect the late phase liver regeneration because of the lack of KCs-related angiogenic factors. This theory is confirmed in the following acetaminophen overdose animal model in which the depletion of KCs significantly delays liver structure recovery at the late time point; this detrimental effect is caused by acetaminophen-induced liver sinusoidal endothelial cell injury, which cannot rapidly recover without KCs-related angiogenic factors, leading to the prolonged vascular leakage. The delayed liver regeneration is not caused by impaired hepatocyte proliferation in this acetaminophen overdose model [75]. These evidences suggest that KCs play a complicated role in acetaminophen hepatotoxicity. KCs promote liver injury at early time point by producing pro-inflammatory mediators; these hepatic resident macrophages also have a significant impact on the late phase liver regeneration by affecting liver blood vessel repair via the angiogenic factors during hepatotoxicity.

Conclusions

DAMPs significantly contribute to liver injury and link local tissue damage to systemic inflammation during drug hepatotoxicity. DAMPs are promising mechanistic biomarkers and could also be the potential therapeutic targets for drug hepatotoxicity. DAMPs-triggered sterile inflammation contributes to liver injury at early phase but improves liver regeneration at later phase of acetaminophen hepatotoxicity; therefore, anti-inflammatory therapy would be beneficial at early phase but should be avoided at the late phase of acetaminophen toxicity.

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Compliance with ethical requirements This investigation has complete compliance with ethical standards.

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Not applicable for a review article.

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References

1. Tittarelli R, Pellegrini M, Scarpellini MG, Marinelli E, Bruti V, di Luca NM, Busardo FP, Zaami S. Hepatotoxicity of paracetamol and related fatalities. Eur Rev Med Pharmacol Sci. 2017;21(1 Suppl):95–9.
2. Iorga A, Dara L, Kaplowitz N. Drug-induced liver injury: cascade of events leading to cell death, apoptosis or necrosis. Int J Mol Sci. 2017;9:18 **(Ijms 18051018)**.
3. Du K, Ramachandran A, Jaeschke H. Oxidative stress during acetaminophen hepatotoxicity: source, pathophysiological role and therapeutic potential. Redox Biol. 2016;10:148–56.
4. Kang R, Lotze MT, Zeh HJ, Billiar TR, Tang D. Cell death and DAMPs in acute pancreatitis. Mol Med. 2014;20:466–77.
5. Yang R, Zou XP, Tenhunen J, Tonessen TI. HMGB1 and extracellular histones significantly contribute to systemic inflammation and multiple organ dysfunctions in acute liver failure. Mediators Inflamm. 2017;2017:5928078.
6. Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol. 2007;81:1–5.
7. Bertheloot D, Latz E. HMGB1, IL-1a, IL-33 and S100 proteins: dual-function alarmins. Cell Mol Immunol. 2017;14:43–64.
8. Yang H, Wang H, Levine YA, Gunasekaran MK, Wang Y, Addorisio M, Zhu S, Li W, Li J, de Kleijn DP, Olofsson PS, Warren HS, He M, Al-Abed Y, Roth J, Antoine DJ, Chavan SS, Andersson U, Tracey KJ. Identification of CD163 as an anti-inflammatory receptor for HMGB1-haptoglobin complexes. JCI Insight. 2016;1:pii:e85375.
9. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature. 2002;418:191–5.
10. Bianchi ME, Manfredi AA. High mobility group B1 (HMGB1) protein at the crossroads between innate and adaptive immunity. Immunol Rev. 2007;220:35–46.
11. Yang H, Hreggvidsdottir HS, Palmblad K, Wang H, Ochani M, Li J, Lu B, Chavan S, Rosas-Ballina M, Al-Abed Y, Akira S, Bierhaus A, Erlandsson-Harris H, Andersson U, Tracey KJ. A critical cysteine is required for HMGB1 binding to toll-like receptor 4 and activation of macrophage cytokine release. PNAS. 2010;26:11942–7.
12. Gero D, Szoleczky P, Modis K, Pribis JP, Al-Abed Y, Yang H, Chavan S, Billiar TR, Tracey KJ, Szabo C. Identification of pharmacological modulators of HMGB1-induced inflammatory response by cell-based screening. PLoS One. 2013;8:e65994.
13. Zhang Y, Li W, Zhu S, Jundoria A, Li J, Yang H, Fan S, Wang P, Tracey KJ, Sama AE, Wang H. Tanshinone IIA sodium sulfonate facilitates endocytic HMGB1 uptake. Biochem Pharmacol. 2012;84:1492–500.
14. Cai B, Deitch EA, Ulloa L. Novel insights for systemic inflammation in sepsis and hemorrhage. Mediators Inflamm. 2010;2010:642462.
15. Tadie JM, Bae HB, Jiang S, Park DW, Bell CP, Yang H, Pittet JF, Tracey KJ, Thannickal VJ, Abraham E, Zmijewski JW. HMGB1 promotes neutrophil extracellular trap formation through interactions with toll-like receptor 4. Am J Physiol Lung Cell Mol Physiol. 2013;304:L342–9.
16. Valdes-Ferrer SI, Papoin J, Dancho ME, Olofsson P, Li J, Lipton JM, Avancena P, Yang H, Zou YR, Chavan SS, Volpe BT, Gardenghi S, Rivella S, Diamond B, Andersson U, Steinberg BM, Blanc L, Tracey KJ. HMGB1 mediates anemia of inflammation in murine sepsis survivors. Mol Med 2015. https://doi.org/10.2119/molmed.2015.00243
17. Yang R, Zhang S, Cotoia A, Oksala N, Zhu S, Tenhunen J. High mobility group B1 impairs hepatocyte regeneration in acetaminophen hepatotoxicity. BMC Gastroenterol. 2012;12:45.
18. Yang R, Zou X, Tenhunen J, Zhu S, Kajander H, Koskinen M, Tonesseen TI. Neutralization of HMGB1 is associated with bacterial translocation during acetaminophen hepatotoxicity. BMC Gastroenterol. 2014;14:66.
19. Antoine DJ, Dear JW, Lewis PS, Platt V, Coyle J, Masson M, Thanacoody RH, Gray AJ, Webb DJ, Moggs JG, Bateman DN, Goldring CE, Park BK. Mechanistic biomarkers provide early and sensitive detection of acetaminophen- induced acute liver injury at first presentation to hospital. Hepatology. 2013;58:777–87.
20. Antoine DJ, Jenkins RE, Dear JW, Williams DP, McGill MR, Sharper MR, Craig DG, Simpson KJ, Jaeschke H, Park BK. Molecular forms of HMGB1 and kerarin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity. J Hepatol. 2012;56:1070–9.
21. Majumdar M, Ratho R, Chawla Y, Singh MP. High levels of circulating HMGB1 as a biomarker of acute liver failure in patients with hepatitis E. Liver Int. 2013;33:1341–8.
22. Oshima G, Shinoda M, Tanabe M, et al. Increased plasma levels of high mobility group box 1 in patients with acute liver failure. Eur Surg Res. 2012;48:154–62.
23. Sappington PL, Yang R, Yang H, Tracey KJ, Deluder RL, Fink MP. HMGB1 B box increases the permeability of Caco-2 enterocytic monolayers and impairs intestinal barrier function in mice. Gastroenterology. 2002;123:790–802.
24. Lundback P, Lea JD, Sowinska A, Ottosson L, Furst CM, Steen J, Aulin C, Clarke JI, Kipar A, Klevenvall L, Yang H, Palmblad K, Park BK, Tracey KJ, Blom AM, Andersson U, Antoine DJ,

Erlandsson Harris H. A novel high mobility group box 1 neutralizing chimeric antibody attenuates drug-induced liver injury and postinjury inflammation in mice. Hepatology. 2016;64:1699–710.
25. Wang W, Sun L, Deng Y, Tang J. Synergistic effects of antibodies against high-mobility group box 1 and tumor necrosis factor-a on D- (+)- galactosamine hydrochloride/lipopolysaccharide-induced acute liver failure. FEBS J. 2013;280:1409–19.
26. Lei YC, Yang LL, Li W, Luo P, Zheng PF. Inhibition of sphingosine kinase 1 ameliorates acute liver failure by reducing high-mobility group box 1 cytoplasmic translocation in liver cells. World J Gastroenterol. 2015;21:13055–63.
27. Venereau E, De Leo F, Mezzapelle R, Careccia G, Musco G, Bianchi ME. HMGB1 as a biomarker and drug target. Pharmacol Res. 2016;111:534–44.
28. Kocsis AK, Szabolcs A, Hofner P, Takacs T, Farkas G, Boda K, Mandi Y. Plasma concentrations of high-mobility group box protein 1, soluble receptor for advanced glycation end-products and circulating DNA in patients with acute pancreatitis. Pancreatology. 2009;9:383–91.
29. Yasuda T, Ueda T, Takeyama Y, Shinzeki M, Sawa H, Nakajima T, Ajiki T, Fujino Y, Suzuki Y, Kuroda Y. Significant increase of serum high-mobility group box chromosomal protein 1 levels in patients with severe acute pancreatitis. Pancreas. 2006;33:359–63.
30. Zhang T, Xia M, Zhan Q, Zhou Q, Lu Q, An F. Sodium butyrate reduces organ injuries in mice with severe acute pancreatitis through inhibiting HMGB1 expression. Dig Dis Sci. 2015;60:1991–9.
31. Lau A, Wang S, Liu W, Haig A, Zhang Z, Jevnikar AM. Glycyrrhizic acid ameliorates HMGB1-mediated cell death and inflammation after renal ischemia reperfusion injury. Am J Nephrol. 2014;40:84–95.
32. Hu Y, Pai MH, Yeh CL, Hou YC, Yeh SL. Glutamine administration ameliorates sepsis-induced kidney injury by downregulating the high-mobility group box protein-1-mediated pathway in mice. Am J Physiol Renal Physiol. 2012;302:F150–8.
33. Sawa H, Ueda T, Takeyama Y, Yasuda T, Shinzeki M, Nakajima T, Kuroda Y. Blockade of high mobility group box-1 protein attenuates experimental severe acute pancreatitis. World J Gastroenterol. 2006;12:7666–70.
34. Kao RL, Xu X, Xenocostas A, Parry N, Mele T, Martin CM, Rui T. Induction of acute lung inflammation in mice with hemorrhagic shock and reperfusion: role of HMGB1. J Inflamm (Lond). 2014;11:30–7.
35. Entezari M, Javdan M, Antoine DJ, Morrow DM, Sitapara RA, Patel V, Wang M, Sharma L, Gorasiya S, Zur M, Wu W, Li J, Yang H, Ashby CR, Thomas D, Wang H, Mantell LL. Inhibition of extracellular HMGB1 attenuate hyperoxia-induced inflammatory acute lung injury. Redox Biol. 2014;2:314–22.
36. Luan Z, Zhang X, Yin X, Ma X, Zhang H, Zhang C, Guo R. Downregulation of HMGB1 protects against the development of acute lung injury after severe acute pancreatitis. Immunobiology. 2013;218:1261–70.
37. Fink MP. Leaky gut hypothesis: a historical perspective. Crit Care Med. 1990;18:579–80.
38. de Jong PR, Gonzalez-Navajas JM, Jansen NJ. The digestive tract as the origin of systemic inflammation. Crit Care. 2016;20:279.
39. Yang R, Tenhunen J, Tonnessen TI. HMGB1 and histones play a significant role in inducing systemic inflammation and multiple organ dysfunctions in severe acute pancreatitis. Int J Inflam. 2017;2017:1817564.
40. Fanous M, Phillips AJ, Windsor JA. Mesenteric lymph: the bridge to future management of critical illness. JOP J Pancreas. 2007;8:374–99.
41. Runkel N. Bacterial translocation in acute pancreatitis. Dig Surg. 1996;13:269–72.
42. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology. 2000;32:734–9.
43. Allam R, Kumar SVR, Darisipudi MN, Anders HJ. Extracellular histones in tissue injury and inflammation. J Mol Med. 2014;92:465–72.
44. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, Triantafyllou E, Bernal TV, Auzinger G, Shawcross D, Eefsen M, Bjerring PN, Clemmesen JO, Hockerstedt K, Frederiksen HJ, Hansen BA, Antoniades CG, Wendon J. High-volume plasma exchange in patients with acute liver failure: an open randomized controlled trial. J Hepatol. 2016;64:69–78.
45. Xu J, Zhang X, Monestier M, Esmon NL, Esmon CT. Extracellular histones are mediators of death through TLR2 and TLR4 in mouse fatal liver injury. J Immunol. 2011;187:2626–31.
46. Wen Z, Lei Z, Yao L, Jiang P, Gu T, Ren F, Liu Y, Gou C, Li X, Wen T. Circulating histones are major mediators of systemic inflammation and cellular Injury in patients with acute liver failure. Cell Death Dis. 2016;7:e2391.
47. Li X, Gou C, Yao L, Lei Z, Gu T, Ren F, Wen T. Patients with HBV-related acute-on-chronic liver failure have increased concentrations of extracellular histones aggravating cellular damage and systemic inflammation. J Viral Hepatol. 2017;24:59–67.
48. Huang H, Tohme S, Al-khafaji AB, Tai S, Loughran P, Chen L, Wang S, Kim J, Billiar T, Wang Y, Tsung A. Damage-associated molecular pattern-activated neutrophil extracellular trap exacerbates sterile inflammatory liver injury. Hepatology. 2015;62:600–14.
49. Xu J, Zhang X, Pelayo R, et al. Extracellular histones are major mediators of Death in sepsis. Nature Med. 2009;15:1318–21.
50. Wen Z, Liu Y, Li F, Ren F, Chen D, Li X, Wen T. Circulating histones exacerbate inflammation in mice with acute liver failure. J Cell Biochem. 2013;114:2384–91.
51. Rosin DL, Okusa MD. Dying cells and extracellular histones in AKI: beyond a NET effect? J Am Soc Nephrol. 2012;23:1275–7.
52. Allam R, Scherbaum CR, Darisiputi MN, Mulay SR, Hagele H, Lichtnekert J, Hagemann JH, Schwarzenberger C, et al. Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4. J Am Soc Nephrol. 2012;23:1375–88.
53. Bosmann M, Grailer JJ, Ruemmler R, Russkamp NF, Zetoune FS, Sarma JV, Standiford TJ, Ward PA. Extracellular histones are essential effector of C5aR- and C5L2-mediated tissue damage and inflammation in acute lung injury. FASEB J. 2013;27:5010–21.
54. De Meyer SF, Suidan GL, Fuchs TA, Monestier M, Wagner DD. Extracellular chromatin is an important mediator of ischemic stroke in mice. Arterioscler Thromb Vasc Biol. 2012;32:1884–91.
55. Imaeda AB, Watanabe A, Sohail MA, Mahmood S, Mohamadnejad M, Sutterwala FS, Flavell RA, Mehal WZ. Acetaminophen-induced hepatotoxicity in mice is dependent on TLR9 and NALP3 inflammasome. J Clin Invest. 2009;119:305–14.
56. Araujo AM, Antunes MM, Mattos MS, Diniz AB, Alvarenga DM, Nakagaki BN, Carvalho E, Lacerda VAS, Carvalho-Gontijo R, Goulart J, Mafra K, Freitas-Lopes MA, Oliveira HMC, Dutra CM, David BA, Mendes Silva A, Quesniaux V, Ryffel B, Oliveira SC, Barber GN, Mansur DS, Cunha TM, Rezende RM, Oliveira AG, Menezes GB. Liver immune cells release type 1 interferon due to DNA sensing and amplify liver injury from acetaminophen overdose. Cells. 2018;7:pii:E88. https://doi.org/10.3390/cells7080088.
57. Ding Y, Li Q, Xu Y, Chen Y, Deng Y, Zhi F, Qian K. Attenuating oxidative stress by paeonol protected against acetaminophen-induced hepatotoxicity in mice. PLoS One. 2016;11:e0154375.

58. Xie W, Wang M, Chen C, Zhang X, Melzig MF. Hepatoprotective effect of isoquercitrin against acetaminophen-induced liver injury. Life Sci. 2016;152:180–9.
59. Wang W, Sun L, Deng Y, Tang J. Synergistic effects of antibodies against high-mobility group box 1 and tumor necrosis factor-a on D- (+) galactosamine hydrochloride/lipopolysaccharide-induced acute liver failure. FEBS J. 2013;280:1409–19.
60. Fausto N. Liver regeneration. J Hepatol. 2000;32:19–31.
61. Chiu H, Gardner CR, Dambach DM, Durham SK, Briuingham JA, Laskin JD, Laskin DL. Role of tumor necrosis factor receptor 1 (p55) in hepatocyte proliferation during acetaminophen-induced toxicity in mice. Toxicol Appl Pharmacol. 2003;193:218–27.
62. Yamada Y, Kirillova I, Peschon JJ, Fausto N. Initiation of liver growth by tumor necrosis factor: deficient liver regeneration in mice lacking type 1 tumor necrosis factor receptor. Proc Natl Acad Sci. 1997;94:1441–6.
63. Mehendale HM. Tissue repair: an important determinant of final outcome of toxicant-induced injury. Toxicol Pathol. 2005;33:41–51.
64. Akerman P, Coto P, Yang SQ, McClain C, Nelson S, Bagby GJ, Diehl AM. Antibodies to tumor necrosis factor-alpha inhibit liver regeneration after partial hepatectomy. Am J Physiol. 1992;263:G579–85.
65. Cataldegirmen G, Zeng S, Feirt N, Ippagunta N, Dun H, Qu W, Lu Y, Rong L, Hofmann MA, Kislinger T, Pachydaki SI, Jenkins DG, Weinberg A, Lefkowitch J, Rogiers X, Yan S, Schmidt AM, Emond JC. Rage limits regeneration after massive liver injury by coordinated suppression of TNF-α and NF-κB. JEM. 2005;201:473–84.
66. Lang K, Suttner S, Boldt J, Kumle B, Nagel D. Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery. Can J Anaesth. 2003;50:1009–16.
67. Tamayo E, Alvarez FJ, Alonso O, Castrodeza J, Bustamante R, Gomez-Herreras JI, Florez S, Rodriguez R. The inflammatory response to colloids and crystalloids used for pump priming during cardiopulmonary bypass. Acta Anaesthesiol Scand. 2008;52:1204–12.
68. Deree J, Loomis WH, Wolf P, Coimbra R. Hepatic transcription factor activation and proinflammatory mediator production is attenuated by hypertonic saline and pentoxifylline resuscitation after hemorrhagic shock. J Trauma. 2008;64:1230–8.
69. Yang R, Zhang S, Kajander H, Zhu S, Koskinen ML, Tenhunen J. Ringer's lactate improves liver recovery in a murine model of acetaminophen toxicity. BMC Gastroenterol. 2011;11:125.
70. Yang R, Zou X, Koskinen ML, Tenhunen J. Ethyl pyruvate reduces liver injury at early phase but impairs regeneration at late phase in acetaminophen overdose. Crit Care. 2012;16:R9.
71. Zeng T, Zhang CL, Xiao M, Yang R, Xie KQ. Critical roles of Kupffer cells in the pathogenesis of alcoholic liver disease: from basic science to clinical trials. Front Immunol. 2016;7:538.
72. Ju C, Reilly TP, Bourti M, Radonovich MF, Brady JN, George JW, Pohl LR. Protective role of Kupffer cells in acetaminophen-induced hepatic injury in mice. Chem Res Toxicol. 2002;15:1504–13.
73. Goldin RD, Ratnayaka ID, Breach CS, Brown IN, Wickramasinghe SN. Role of microphages in acetaminophen (paracetamol)-induced hepatotoxicity. J Pathol. 1996;179:432–5.
74. Yang Q, Shi Y, He J, Chen Z. The evolving story of macrophages in acute liver injury. Immunol Lett. 2012;147:1–9.
75. You Q, Holt M, Yin H, Li G, Hu C, Ju C. Role of hepatic resident and infiltrating macrophages in liver repair after acute injury. Biochem Pharmacol. 2013;86:836–43.