

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Novel Mechanism Supporting Therapeutic Effects of Glycyrrhizin in Acute or Chronic Hepatitis

Noriyuki Kuroda and Tetsuji Sato

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/67078>

Abstract

Glycyrrhizin (GL) isolated from the roots of licorice plant (*Glycyrrhiza glabra* L.) has been traditionally used for treating peptic ulcer, hepatitis, and pulmonary bronchitis. In addition to the protective effects of GL against liver injury or cancer proliferation by the membrane stabilization or via progesterone-receptor membrane component 1 (PGRMC1), the present chapter reports its new therapeutic mechanism through high-mobility group protein 1 (HMGB1) to which GL directly binds. In this study, we evaluated inflammation-promoting activity of HMGB1 and blockade of extracellular release of HMGB1 by GL in lipopolysaccharide (LPS)/D-galactosamine (GalN)-triggered mouse liver injury. In this experimental hepatitis model, apoptotic response of hepatocytes through the binding of HMGB1 protein to Glutathione transferase omega 1 (*Gsto1*), an apoptosis-associated gene, promoter region is caused, serum AST and ALT activities significantly increased, and GL-treatment prevented the apoptosis and inflammatory infiltrates induced with LPS/GalN-injection by disturbing the binding of HMGB1 protein to *Gsto1* promoter sequence. Analysis with chromatin immunoprecipitation (ChIP)-assay revealed inhibiting the binding of HMGB1 protein to *Gsto1* by the binding of GL to HMGB1.

Keywords: glycyrrhizin, liver injury, PAMPs, DAMPs, HMGB1

1. Introduction

Glycyrrhizin (GL), a triterpenoid glycoside isolated from the roots of licorice plant (*Glycyrrhiza glabra* L.), has been traditionally used for treating peptic ulcer, hepatitis, and pulmonary bronchitis. Various pharmacological effects of GL are well known, such as anti-inflammatory [1, 2], anti-allergic [3], and hepatoprotective activity [4–6]. In Japan, Stronger Neo-Minophagen C, the active ingredient of which is GL, has been used as a treatment for over 25 years for patients with chronic hepatitis. Intravenous administration of GL decreases serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients with chronic

hepatitis [7, 8]. The well-defined model of hepatic injury induced by the injection of lipopolysaccharide (LPS)/D-galactosamine (GalN) has been widely used in studies of the mechanisms of human hepatitis. GalN is an aminosugar selectively metabolized by hepatocytes, which induces a depletion of the uridine triphosphate pool and thereby an inhibition of macromolecule (RNA, protein, and glycogen) synthesis in the liver [9]. Combination of LPS and GalN causes specifically hepatic failure in rodent [10]. Under the stimulation by LPS, liver macrophages secrete various pro-inflammatory cytokines including tumor necrosis factor (TNF)- α which is a terminal mediator for apoptosis, subsequently leading to hepatic necrosis [11–14]. The hepatic lesion in this model resembles that of human hepatitis since the up-regulation of TNF- α level and hepatic apoptosis have been reported as pathogenic symptoms in human hepatitis. GL, an aqueous extract of licorice root, has been used for the treatment of chronic hepatitis to reduce the liver inflammation [15–17], but its effects on acute hepatic injury have been unclear. A recent report showed that Y-40138, a synthetic compound, inhibits liver injury evoked by LPS/GalN through the suppression of TNF- α and monocyte chemoattractant protein-1 and the augmentation of IL-10 [18]. GL prevents anti-Fas antibody-induced mouse liver injury but has no effect on the upregulation of TNF- α mRNA expression in the liver [6]. In our previous study [19], we reported that levels of serum of cytokines such as TNF- α , interleukin (IL)-6, IL-10, IL-12, and IL-18 as well as those of serum ALT significantly increased after administration of LPS/GalN. GL had no effect on the production of TNF- α , IL-6, IL-10, and IL-12, whereas it significantly inhibited the increase in ALT levels and IL-18 production. We have so far indicated that the inhibitory effect of GL is different from that of inhibitor for TNF- α production, such as Y-40138 [18] and bicyclol, a new synthetic anti-hepatitis drug [20].

High-mobility group proteins (HMGBs) possess a unique DNA-binding domain that is subject to transcriptional regulation [21]. One of these proteins, HMGB1 (amphoterin), can be secreted into the extracellular milieu as a late-acting mediator of LPS-induced or sepsis-induced lethality in mice [22]. Although HMGB1 is a non-histone nuclear protein, it is passively released from necrotic cells [23] or actively secreted from stress-received cells such as monocytes/macrophages as an inflammatory cytokine in response to endotoxin, tumor necrosis factor (TNF)- α , or interleukin (IL)-1 β [22, 24–26]. HMGB1, which was released into the intravascular area, has great potential as a local inflammatory activator through intensifying the release of cytokines and chemokines from stimulated cells [27] and interact with endothelial cells by up-regulating surface receptors and causing the secretion of soluble pro-inflammatory mediators [28]. Extracellular HMGB1 works properly as a damage-associated molecular patterns (DAMPs) molecule and increases powers of pro-inflammatory signaling paths by activating pattern recognition receptors (PRRs) including toll-like receptor 4 (TLR4) and/or the receptor for advanced glycation end-products (RAGE) [25, 29]. Increasing evidence suggests that HMGB1 may also operate so as to assist the progress of the recognition of other immune co-activators such as LPS, DNA, and IL-1 by being excessively desirous of the binding to these molecules [30–32]. However, the mechanisms by which GL inhibits inflammation induced with pathogen-associated molecular patterns (PAMPs) such as LPS or endogenous DAMPs such as HMGB1 have not been clearly revealed.

Previous results have suggested that glycyrrhizin (GL) and glycyrrhetic acid (GA) exert their protective effects by the membrane stabilization which results in inhibiting the prolongation of oxidative stress [33]. Furthermore, progesterone-receptor membrane component 1 (PGRMC1) was proposed as a new target protein for GL. PGRMC1 is a haem-containing protein that inter-

acts with epidermal growth factor (EGFR) and cytochrome P450 to regulate cancer proliferation and chemoresistance [34]. GL is thought to reduce cancer proliferation via PGRMC1. On the other hand, a research work utilizing nuclear magnetic resonance (NMR) and fluorescence methods revealed the supplementary mechanism by which GL directly binds to HMGB1 and suppresses the HMGB1 chemoattractant and mitogenic activities [35]. Recent studies, furthermore, have reported that GL reduces inflammatory infiltrates by inhibiting the cellular proliferation and migration, and formation of blood vessels induced by HMGB1 [36]. In this chapter, we evaluated the underlying new mechanism supporting various pharmacological effects of GL on the basis of upcoming data of our experiment on hepatitis induced by an injection of LPS/GalN.

2. Results and discussion

In the present study, we explored inflammation-promoting activity of HMGB1 and blockade of extracellular release of HMGB1 by GL in LPS/GalN-triggered mouse liver injury. Male BALB/c mice were intravenously injected with LPS/GalN. At 1–10 h after LPS/GalN treatment, mice were anesthetized to collect blood by heart puncture, and serum transaminase and HMGB1 were evaluated. Intraperitoneal administration of GL was performed 30 min before treatment. Effects of GL on liver damage were examined 8 h after stimulation with endotoxin. The injection of LPS/GalN significantly increases serum AST and ALT activities as compared with controls. The enhancement of AST and ALT levels is significantly suppressed by an intraperitoneal administration of GL (**Figure 1**; [19, 37, 38]). Administration of LPS/GalN precipitate tissue injury associated with time-dependent alteration in HMGB1 serum levels. Immunohistochemistry with antibodies to HMGB1 reveals a distinct nuclear expression in the hepatocytes of control mice. Immunoreactivity to HMGB1 begins to be suppressed in the nuclei 6 h after administration of LPS/GalN. At 8 h nuclear immunoreactive products are remarkably reduced and extracellular HMGB1 expression is found exclusively in the pericentral foci. Double-immunofluorescence staining for HMGB1/F4/80 or HMGB1/CD11c demonstrates that some cell populations of F4/80⁺ and CD11c⁺ cells located in the inflammatory foci are immunolabeled simultaneously with HMGB1 8 h after stimulation with LPS/GalN [39]. The GL-treatment significantly reduces the serum levels of ALT, AST, and HMGB1 besides the strong inhibition of inflammatory tissue damage, and cytoplasmic and extracellular immunoreactive-response to both the HMGB1 and acetylated-lysine. The acetylation of HMGB1 is physiologically involved in regulating HMGB1 DNA binding properties along with the subcellular location. The lysine residues of HMGB1 between 27 and 43 represent functional nuclear localizing signals. An administration of GL brings about a significant decrease in the number of apoptotic hepatocytes labeled with TUNEL-method. On the basis of these results, we have identified an apoptosis-associated gene, Glutathione transferase omega 1 (*Gsto1*), using microarray analysis and real-time PCR (**Figure 2**). In addition, the chromatin immunoprecipitation (ChIP)-assay have revealed the binding of HMGB1 protein to *Gsto1* promoter sequence and the remarkable decrease in the volume of bound HMGB1 protein by administration of GL (**Figure 3**). Our findings claim that GL treatment might prevent the apoptosis and inflammatory infiltrate caused with LPS/GalN-treatment by disturbing the binding of HMGB1 protein to *Gsto1* promoter sequence. We provide *in vivo* evidence showing that HMGB1 is involved in the apoptosis of hepatocytes caused by LPS/GalN-treatment and administration of GL significantly improves hepatic injury,

in parallel with suppression of exaggerated apoptotic cell death and enhanced expression of regeneration mediator. Several recent investigations including our research [40] have reported that GL may protect against liver injury by reducing the expression of HMGB1, a mediator of inflammation [41, 42]. The induction of liver injury in mice by LPS/GalN represents a promising animal model for elucidating the mechanism of clinical dysfunction and for evaluating the efficacy of hepatoprotectives. The liver injury induced by LPS has been reported to be abrogated by treatment with anti-TNF- α mAb or p55 TNF receptors in mice [43–45]. TNF- α can induce apoptosis of hepatocytes at an early stage in LPS/GalN-induced liver injury, and neutrophil transmigration can represent a critical step leading to necrosis of hepatocytes at a later stage [46, 47]. In our study [19], the serum levels of TNF- α were markedly increased 0.5–1 h after LPS/GalN-treatment. Treatment with anti-TNF- α antibody reduced the elevated ALT level by LPS/GalN. Thus, it appears that TNF- α plays an important role in the pathogenesis of this model. There is evidence for the cytoprotection by IL-6 of liver injury induced by LPS [48]. In addition, both endogenous and exogenous IL-10 protect against LPS/GalN-induced liver injury [49]. Others have reported that at a 2-h time-point, IL-12 is increased in plasma of mice treated with LPS/GalN [13]. We have confirmed that the serum levels of IL-6, IL-10, and IL-12 can reach a maximum by 2 h after LPS/GalN treatment [19]. GL had no effect on the production of TNF- α , IL-6, IL-10, and IL-12 in the same model mice, whereas it significantly inhibited increase in ALT levels.

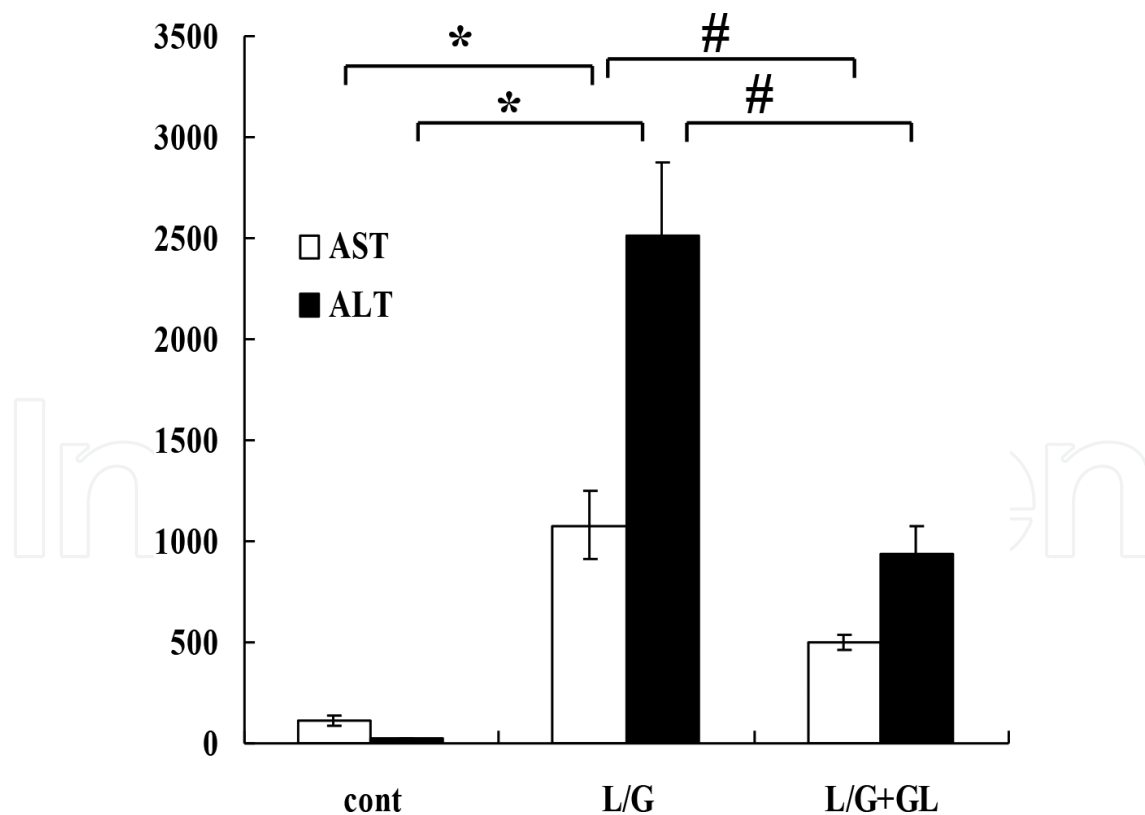


Figure 1. The effect of GL on serum AST and ALT levels at 8 h after administration of LPS/D-GalN. Increased serum AST and ALT levels are significantly inhibited by combined treatment with LPS/D-GalN + GL (L/G + GL) compared with mice treated with L/G. *Significant difference compared with 0 h or control ($P < 0.05$); #Significant difference between L/G and L/G + GL ($P < 0.05$); each value represents the mean \pm SEM of six mice (Cited from Ref. [38]).

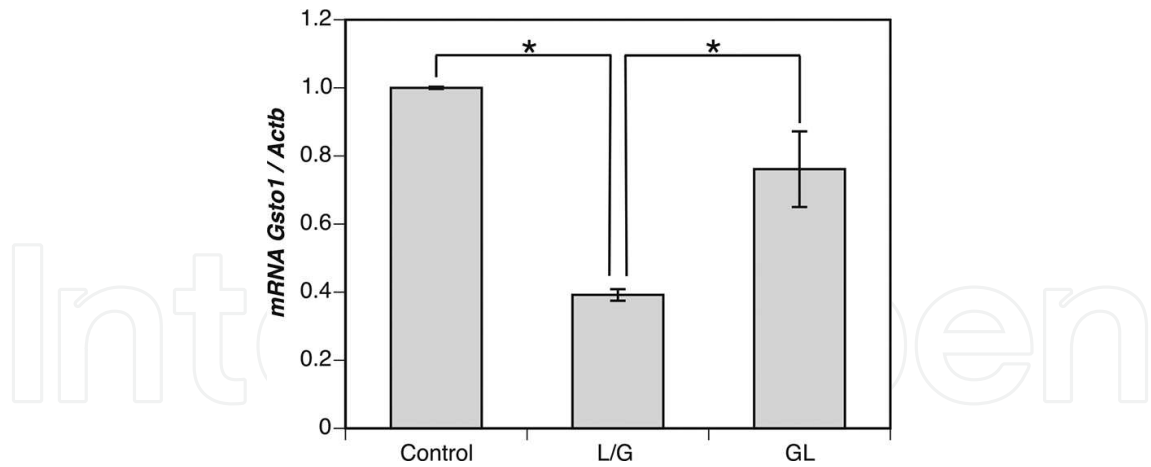


Figure 2. mRNA expression of *Gsto1* gene involved in apoptosis by LPS/GalN-treatment. After an injection of LPS/GalN, the expression level of *Gsto1* mRNAs is significantly decreased. The expression level of *Gsto1* mRNA is significantly recovered by administration of GL. *Significant difference between two groups (Control versus LPS/GalN or LPS/GalN versus GL + LPS/GalN) approved ($P < 0.05$). L/G: LPS/GalN, GL: GL + LPS/GalN (Cited from Ref. [40]).

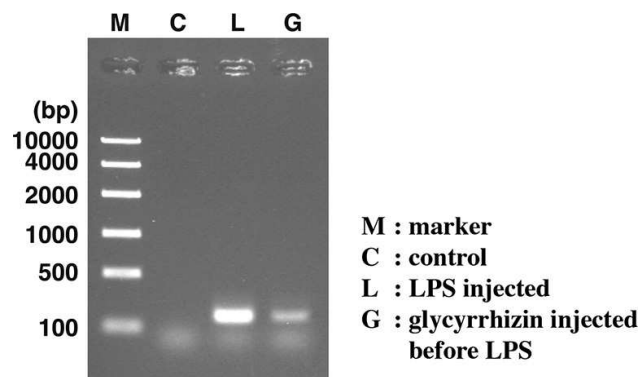


Figure 3. Analysis of HMGB1-binding to *Gsto1* with chromatin immunoprecipitation (ChIP)-assay. Hmgb1 protein intensely binds to *Gsto1* promoter sequence in LPS/GalN-induced liver injury and an administration of GL remarkably inhibits the binding of Hmgb1 to *Gsto1* promoter sequence. M: marker, C: control, L: LPS/GalN, G: GL + LPS/GalN (Cited from Ref. [40]).

HMGB1 is a multifunctional protein: the earliest studies reported it as a nonhistone DNA-binding nuclear protein. HMGB1 binds to DNA in a sequence-independent manner and changes the structure of DNA so as to assist the progress of transcription, replication, and repair [50, 51]. These functions are essential for survival, as HMGB1-deficient mice die of hypoglycemia within 24 h after birth [52]. Recent researches have identified HMGB1 as a new inflammatory factor and a late mediator of endotoxin lethality in mice [53]. Extracellularly released HMGB1 mobilizes a great number of various physiological reactions in different cell types [54]. HMGB1 may be released both through active secretion from various cells, including activated monocytes/macrophages [22], neutrophils [55], and endothelial cells [56], and passively from necrotic or damaged cells [23]. HMGB1 is released as a danger signal from damaged cells [24]. Even when cellular integrity is maintained, hepatocyte HMGB1 expression increases markedly after noxious stimuli [13, 24]. In our experiment, immunohistochemistry revealed

HMGB1 overexpression was found predominantly in the inflammatory foci located close to the central veins, that is, in areas most susceptible to LPS/GalN-treatment.

3. Conclusion

Apoptotic response of hepatocytes through the binding of HMGB1 protein to *Gsto1* promoter region is caused in this experimental hepatitis model and GL-treatment prevents the apoptosis and inflammatory infiltrates caused with LPS/GalN-injection by disturbing the binding of HMGB1 protein to *Gsto1* promoter sequence. The present findings claim a new mechanism supporting therapeutic effects of GL in hepatitis (**Figure 4**).

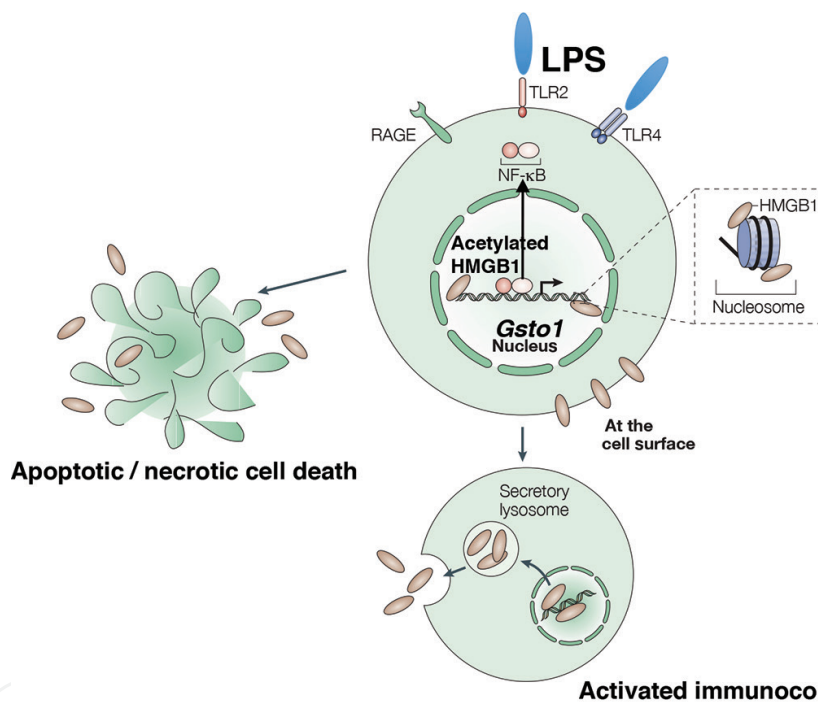


Figure 4. Action point of acetylated HMGB1. An administration of GL suppresses apoptotic cell death through inhibiting the binding of Hmgb1 to *Gsto1* (Scheme modified from Nature Reviews Immunology 2005:5:334).

Author details

Noriyuki Kuroda and Tetsuji Sato*

*Address all correspondence to: sato-t@tsurumi-u.ac.jp

Department of Anatomy, Tissue, and Cell Biology, School of Dental Medicine, Tsurumi University, Yokohama, Japan

References

- [1] Ohuchi K, Kamada Y, Levine L, Tsurufuji S. Glycyrrhizin inhibits prostaglandin E2 production by activated peritoneal macrophages from rats. *Prostaglandins and Medicine*. 1981;**7**:457–463.
- [2] Okimasu E, Moromizato Y, Watanabe S, Sasaki J, Shiraishi N, Morimoto YM, Miyahara M, Utsumi K. Inhibition of phospholipase A2 and platelet aggregation by glycyrrhizin, an antiinflammation drug. *Acta Medica Okayama*. 1983;**37**:385–391.
- [3] Kuroyanagi T, Saito M. Effect of prednisolone and glycyrrhizin on passive transfer in experimental allergic encephalomyelitis. *Arerugi*. 1966;**15**:67–74.
- [4] Nose M, Ito M, Kamimura K, Shimizu M, Ogihara Y. A comparison of the antihepatotoxic activity between glycyrrhizin and glycyrrhetic acid. *Planta Medica*. 1994;**60**:136–139.
- [5] Okamoto T, Kanda T. Glycyrrhizin protects mice from concanavalin A-induced hepatitis without affecting cytokine expression. *International Journal of Molecular Medicine*. 1999;**4**:149–152.
- [6] Okamoto T. The protective effect of glycyrrhizin on anti-Fas antibody-induced hepatitis in mice. *European Journal of Pharmacology*. 2000;**387**:229–232.
- [7] Arase Y, Ikeda K, Murashima N, Chayama K, Tsubota A, Koida I, Suzuki Y, Saitoh S, Kobayashi M, Kumada H. The long term efficacy and glycyrrhizin in chronic hepatitis C patients. *Cancer*. 1997;**79**:1494–1500.
- [8] Ikeda K, Arase Y, Kobayashi M, Saitoh S, Someya T, Hosokawa T, Senzaki H, Akuta N, Suzuki Y, Suzuki F, Kumada H. A long-term glycyrrhizin injection therapy reduces hepatocellular carcinogenesis rate in patients with interferon-resistant active chronic hepatitis C: a cohort study of 1249 patients. *Digestive Diseases and Sciences*. 2006;**51**:603–609.
- [9] Decker K, Keppler D. Galactosamine hepatitis: key role of the nucleotide deficiency period in the pathogenesis of cell injury and cell death. *Reviews of Physiology, Biochemistry and Pharmacology*. 1974;**71**:77–106.
- [10] Galanos C, Freudenberg MA, Reutter W. Galactosamine-induced sensitization to the lethal effects of endotoxin. *Proceedings of the National Academy of Sciences of the United States of America*. 1979;**76**:5939–5943.
- [11] Tiegs G, Wolter M, Wendel A. Tumor necrosis factor is a terminal mediator in galactosamine/endotoxin-induced hepatitis in mice. *Biochemical Pharmacology*. 1989;**38**:627–631.
- [12] Leist M, Gantner F, Bohlinger I, Toegs G, Gertmann PG, Wendel A. Tumor necrosis factor-induced hepatocyte apoptosis precedes liver failure in experimental murine shock models. *The American Journal of Pathology*. 1995;**146**:1220–1234.
- [13] Sass G, Heinlein S, Agli A, Bang R, Schumann J, Tiegs G. Cytokine expression in three mouse model of experimental hepatitis. *Cytokine*. 2002;**19**:115–120.

- [14] Morikawa A, Sugiyama T, Kato Y, Koide N, Jiang G, Takahashi K, Tamada Y, Yokochi T. Apoptotic cell death in the response of D-galactosamine-sensitized mice to lipopolysaccharide as an experimental endotoxic shock model. *Infection and Immunity*. 1996; **64**:734–738.
- [15] Takahara T, Watanabe A, Shiraki K. Effects of glycyrrhizin on hepatitis B surface antigen: a biochemical and morphological study. *Journal of Hepatology*. 1994; **21**:601–609.
- [16] Ito A, Hayashi N, Katayama K, Hagiwara H, Kasahara A, Kashiwagi T, Yoshihara H, Fusamoto H, Kamada T. Effect of glycyrrhizin on viral replication and quasispecies in patients with type C chronic hepatitis. *International Hepatology Communications*. 1997; **6**:233–238.
- [17] Yoshikawa M, Matsui Y, Kawamoto H, Umemoto N, Oku K, Koizumi M, Yamao J, Kuriyama S, Nakano H, Hozumi N, Ishizaka S, Fukui H. Effects of glycyrrhizin on immune-mediated cytotoxicity. *Journal of Gastroenterology and Hepatology*. 1997; **12**:243–248.
- [18] Fukuda T, Mogami A, Tanaka H, Yoshikawa T, Hisadome M, Komatsu H. Y-40138, a multiple cytokine production modulator, protects against D-galactosamine and lipopolysaccharide-induced hepatitis. *Life Sciences*. 2006; **79**:822–827.
- [19] Yoshida T, Abe K, Ikeda T, Matsushita T, Wake K, Sato T, Sato To, Inoue H. Inhibitory effect of glycyrrhizin on lipopolysaccharide and D-galactosamine-induced mouse liver injury. *European Journal of Pharmacology*. 2007; **576**:136–142.
- [20] Wang H, Li Y. Protective effect of bicyclol on acute hepatic failure induced by lipopolysaccharide and D-galactosamine in mice. *European Journal of Pharmacology*. 2006; **534**:194–201.
- [21] Bustin M, Hopkins RB, Isenberg I. Immunological relatedness of high mobility group chromosomal proteins from calf thymus. *The Journal of Biological Chemistry*. 1978; **253**:1694–1699.
- [22] Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che JH, Ivanova S, Borovikova L, Manogure LR, Faist E, Abraham E, Andersson U, Molina PR, Abumrad NN, Sama A, Tracey KJ. HMG-1 as a late mediator of endotoxin lethality in mice. *Science*. 1999; **285**:248–251.
- [23] Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature*. 2002; **418**:191–195.
- [24] Tsung A, Sahai R, Tanaka H, Nakao A, Fink MP, Lotze MT, Yang H, Li J, Tracey KJ, Geller DA, Billiar TR. The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion. *The Journal of Experimental Medicine*. 2005; **201**:1135–1143.
- [25] Tsung A, Klune JR, Zhang X, Jeyabalan G, Cao Z, Peng X, Stolz DB, Geller DA, Rosengart MR, Billiar TR. HMGB1 release induced by liver ischemia involves toll-like receptor 4-dependent reactive oxygen species production and calcium-mediated signaling. *The Journal of Experimental Medicine*. 2007; **204**:2913–2923.

- [26] Ilmakunnas M, Tukiainen A, Rauvala H, Arola J, Nordin A, Mäkisalo H, Höckerstedt K, Isoniemi H. High mobility group box 1 protein as a marker of hepatocellular injury in human liver transplantation. *Liver Transplantation*. 2008;**14**:1517–1525.
- [27] Andersson U, Wang H, Palmblad K, Aveberger AC, Bloom O, Erlandsson-Harris H, Janson A, Kokkola R, Zhang M, Yang H, Tracey KJ. High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. *The Journal of Experimental Medicine*. 2000;**192**:565–570.
- [28] Fiuza C, Bustin M, Talwar S, Tropea M, Gerstenberger E, Shelhamer JH, Suffredini AF. Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. *Blood*. 2003;**101**:2652–2660.
- [29] Hori O, Brett J, Slattery T, Cao R, Zhang J, Chen X, Nagashima M, Lundh ER, Vijay S, Nitecki D, Morsert J, Stern D, Schmidt AM. The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. *The Journal of Biological Chemistry*. 1995;**270**:25752–25761.
- [30] Ivanov S, Dragoi A-M, Wang X, Dallacosta C, Louten J, Musco G, Sitia G, Yap GS, Wan Y, Biron CA, Bianchi ME, Wang H, Chu W-M. A novel role for HMGB1 in TLR9-mediated inflammatory responses to CpG-DNA. *Blood*. 2007;**110**:1970–1981.
- [31] Tian J, Avalos AM, Mao S-Y, Chen B, Senthil K, Wu H, Parroche P, Drabic S, Golenbock D, Sirois C, Hua J, An LL, Audoly L, Rosa GL, Bierhaus A, Naworth P, Marshak-Rothstein A, Crow MK, Fitzgerald KA, Latz E, Kiener RA, Coele AJ. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. *Nature Immunology*. 2007;**8**:487–496.
- [32] Sha Y, Zmijewski J, Xu Z, Abraham E. HMGB1 develops enhanced proinflammatory activity by binding to cytokines. *The Journal of Immunology*. 2008;**180**:2531–2537.
- [33] Takayama F, Egashira T, Yamanaka Y. Effects of glycyrrhizin and glycyrrhetic acid on damage to isolated hepatocytes by transient exposure to *tert*-butyl hydroperoxide. *Japanese Pharmacology and Therapeutics*. 2000;**28**:763–770.
- [34] Kabe Y, Nakane T, Koike I, Yamamoto T, Sugiura Y, Harada E, Sugase K, Shimamura T, Ohmura M, Muraoka K, Yamamoto A, Uchida T, Iwata S, Yamaguchi Y, Krayukhina E, Nada M, Handa H, Ishimori K, Uchiyama S, Kobayashi T, Suematsu M. Haem-dependent dimerization of PGRMC1/Sigma-2 receptor facilitates cancer proliferation and chemoresistance. *Nature Communications*. 2016;**7**:11030. doi: 10.1038/ncomms11030
- [35] Mollica L, Marchis FD, Spitaleri A, Dallacosta C, Pennacchini D, Zamai M, Agresti A, Trisciuglio L, Musco G, Bianchi ME. Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. *Chemistry & Biology*. 2007;**14**:431–441.
- [36] Smolarczyk R, Cichoń T, Matuszczak S, Mitrus I, Lesiak M, Kobusińska M, Kamysz W, Jarosz M, Sieroń A, Szala S. The role of glycyrrhizin, an inhibitor of HMGB1 protein, in anticancer therapy. *Archivum Immunologiae et Therapiae Experimentalis*. 2012;**60**:391–399.

- [37] Abe K, Ikeda T, Wake K, Sato T, Inoue H. Glycyrrhizin prevents lipopolysaccharide/D-galactosamine-induced liver injury through down-regulation of matrix metalloproteinase-9 in mice. *Journal of Pharmacy and Pharmacology*. 2008;**60**:91–97.
- [38] Ikeda T, Abe K, Kuroda N, Kida Y, Inoue H, Wake K, Morito M, Sato T. The inhibition of apoptosis by glycyrrhizin in hepatic injury induced by injection of lipopolysaccharide/D-galactosamine in mice. *Archives of Histology and Cytology*. 2008;**71**:163–178.
- [39] Sato T, Yamamoto H, Sasaki C, Wake K. Maturation of rat dendritic cells during intrahepatic translocation evaluated using monoclonal antibodies and electron microscopy. *Cell and Tissue Research*. 1998;**294**:503–514.
- [40] Kuroda N, Inoue K, Ikeda T, Hara Y, Wake K, Sato T. Apoptotic response through a high mobility box 1 protein-dependent mechanism in LPS/GalN-induced mouse liver failure and glycyrrhizin-mediated inhibition. *PLoS One*. 2014;**9**:e92884. doi: 10.1371/journal.pone.0092884
- [41] Mabuchi A, Wake K, Marlini M, Watanabe H, Wheatley AM. Protection by glycyrrhizin against warm ischemia-reperfusion-induced cellular injury and derangement of the microcirculatory blood flow in the rat liver. *Microcirculation*. 2009;**16**:364–376. doi: 10.1080/10739680902796917
- [42] Ogiku M, Kono H, Hara M, Tsuchiya M, Fujii H. Glycyrrhizin prevents liver injury by inhibition of high-mobility group box 1 production by Kupffer cells after ischemia-reperfusion in rats. *Journal of Pharmacology and Experimental Therapeutics*. 2011;**339**:93–98. doi: 10.1124/jpet.111.182592
- [43] Beutler B, Milsark IS, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science*. 1985;**229**:869–871.
- [44] Tracy KJ, Fong Y, Hesse DG, Manogue KR, Lee AT, Kuo GC, Lowry SF, Cerami A. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature*. 1987;**330**:662–664.
- [45] Lesslauer W, Tabuchi H, Gentz R, Brockhaus M, Schlaeger EJ, Grau G, Piguët PF, Pointaire P, Vassalli P, Loetscher H. Recombinant soluble tumor necrosis factor receptor proteins protect mice from lipopolysaccharide-induced lethality. *European Journal of Immunology*. 1991;**21**:2883–2886.
- [46] Tiegs G. Immunotoxicology of host-response-mediated experimental liver injury. *Journal of Hepatology*. 1994;**21**:890–903.
- [47] Chosay JS, Essani NA, Dunn CJ, Jaeschke H. Neutrophil margination and extravasation in sinusoids and venules of liver during endotoxin-induced injury. *The American Journal of Physiology*. 1997;**272**(5 pt 1):G1195–G1200.
- [48] Inoue K, Takano H, Shimada A, Morita T, Yanagisawa R, Sakurai M, Sato M, Yoshino S, Yoshikawa T. Cytoprotection by interleukin-6 against liver injury induced by lipopoly-

saccharide. *International Journal of Molecular Sciences*. 2005;**15**:221–224.

- [49] Louis H, Moine OL, Peny MO, Gulbis B, Nisol F, Goldman M, Deviere J. Hepatoprotective role of interleukin 10 in galactosamine/lipopolysaccharide mouse liver injury. *Gastroenterology*. 1997;**112**:935–942.
- [50] Johns EW. Studies on histone. 8. A degradation product of lysine-rich histone. *Biochemical Journal*. 1964;**93**:161–163.
- [51] Bustin M. Regulation of DNA-dependent activities by the functional motifs of the high-mobility-group chromosomal proteins. *Molecular and Cellular Biology*. 1999;**19**:5237–5246.
- [52] Calogero S, Grassi F, Aguzzi A, Voigtländer T, Ferrier P, Ferrari S, Bianchi ME. The lack of chromosomal protein Hmg1 does not disrupt cell growth but causes lethal hypoglycaemia in newborn mice. *Nature Genetics*. 1999;**22**:276–280.
- [53] Wang Y, Liu J, Wu Y, Luo W, Lin SH, Lin H, Hawk N, Sun T, Guo JQ, Estrov Z, Talpaz M, Champlin R, Arlinghaus RB: Expression of a truncated first exon BCR sequence in chronic myelogenous leukemia cells blocks cell growth and induces cell death. *Cancer Research*. 2001;**61**:4112–4121.
- [54] Yang H, Wang H, Czura CJ, Tracey KJ. The cytokine activity of HMGB1. *Journal of Leukocyte Biology*. 2005;**78**:1–8.
- [55] Ito I, Fukazawa J, Yoshida M. Post-translational methylation of high mobility group box 1 (HMGB1) causes its cytoplasmic localization in neutrophils. *The Journal of Biological Chemistry*. 2007;**282**:16336–16344.
- [56] Mullins GE, Sunden-Cullberg J, Johansson AS, Rouhiainen A, Erlandsson-Harris H, Yang H, Tracey KJ, Rauvala H, Palmblad J, Andersson J, Treutiger CJ. Activation of human umbilical vein endothelial cells leads to relocation and release of high-mobility group box chromosomal protein 1. *Scandinavian Journal of Immunology*. 2004;**60**:566–573.

IntechOpen

