Molecular insights into the multifaceted functions and therapeutic targeting of high mobility group box 1 in metabolic diseases

Zhipeng Tao | My N. Helms | Benjamin C. B. Leach | Xu Wu

1Cutaneous Biology Research Center, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA
2Pulmonary Division, Department of Internal Medicine, University of Utah, Salt Lake City, Utah, USA

Correspondence
Xu Wu and Zhipeng Tao, Cutaneous Biology Research Center, Harvard Medical School, Massachusetts General Hospital, Charlestown, MA 02129, USA.
Emails: xwu@cbrc2.mgh.harvard.edu; ztao@mgh.harvard.edu
My N. Helms, Pulmonary Division, Department of Internal Medicine, University of Utah, Salt Lake City, UT 84132, USA.
Email: my.helms@hsc.utah.edu

Funding information
Melanoma Research Alliance, Grant/Award Number: 812717

Abstract
HMGB1 is a ubiquitously expressed protein localized in nucleus, cytoplasm, as well as secreted into extracellular space. Nuclear HMGB1 binds to DNAs and RNAs, regulating genomic stability and transcription. Cytoplasmic HMGB1 regulates autophagy through binding to core autophagy regulators. Secreted extracellular HMGB1 functions as a ligand to various receptors (RAGE and TLRs, etc.), regulating multiple signalling pathways, such as MAPK, PI3K and NF-κB signalings. Trafficking and localization of HMGB1 across cellular compartments could be regulated by its posttranslational modifications, which fine-tune its functions in metabolic diseases, inflammation and cancers. The current review examines the up-to-date findings pertaining to the biological functions of HMGB1, with focus on its posttranslational modifications and roles in downstream signalling pathways involved in metabolic diseases. This review also discusses the feasibility of targeting HMGB1 as a potential pharmacological intervention for metabolic diseases.

KEYWORDS advanced glycation end products, autophagy, genomic stability, inflammation, toll-like receptors

1 INTRODUCTION

The high mobility group (HMG)-box (HMGB) family belongs to the HMG protein superfamily that plays important roles in modulating chromatin structures. The HMGB family consists of four chromosomal proteins: HMGB1, HMGB2, HMGB3 and HMGB4. HMGB1 is ubiquitously expressed in high abundance (roughly $1 \times 10^6$ molecules per mammalian cell), whereas HMGB2, 3 and 4 are expressed at lower levels with restricted expression patterns.\(^1\)\(^-\)\(^3\) Herein, we summarize the literature reports on the roles of HMGB1 in metabolic diseases and discuss the perspectives of targeting HMGB1 as a potential therapeutic approach.

HMGB1 protein is both a nuclear factor and a secreted protein.\(^4\) In the nucleus, HMGB1 serves as a transcriptional regulator that binds or bends DNAs or RNAs and promotes transcriptional complex assembly on specific gene targets.\(^5\)\(^,\)\(^6\) For example, HMGB1 binds to the promoter region of TNF and promotes the assembly of the repressor NF-κB factor RelB, thus suppressing TNFα expression.\(^7\) Upon infection or injury, HMGB1 has been shown to translocate from nucleus to the cytoplasm and could also be secreted by activated immune cells.\(^8\) In addition, HMGB1 can be secreted by various cells, including hepatocytes, keratinocytes and granulocytes, under necrosis, DNA damage or oxidative stress.\(^9\)\(^-\)\(^12\) Once secreted, HMGB1 functions as a ligand and binds to the receptor for advanced
glycation end products (RAGE), toll-like receptors (TLRs) and C-X-C Motif Chemokine Receptor 4 (CXCR4), playing important roles in regulation of inflammation and immune responses.13

HMGB1 consists of 215 amino acids, organized into two high mobility group boxes, which function as DNA-binding domains and an acidic C-terminus, respectively (Figure 1). It has been reported that several serine residues of HMGB1, including Ser39, Ser53 and Ser181, could be phosphorylated by protein kinase C zeta (PKC ζ), enhancing HMGB1 secretion.14 HMGB1 is also hyperacetylated at multiple lysine residues near the nuclear localization sequence (NLS) (Figure 1), and such posttranslational modification of lysine residues is affected by JAK/STAT1 signalling.11,15,16 The molecular mechanism responsible for dynamic acetylation and deacetylation of HMGB1 remains unclear and requires further investigation. Poly(ADP-ribose) polymerase-1 (PARP-1)-induced poly(ADP-ribose)ylation of HMGB1 synergizes with acetylation and ultimately leads to HMGB1 secretion under LPS stimulation.11 In addition, HMGB1 could be N-glycosylated at Asn37, Asn134 and Asn135, which is critical for promoting HMGB1 secretion.17 However, inter-plays between different posttranslational modifications of HMGB1 have not been fully studied, which warrant further investigation.

2 | REDOX REGULATION OF HMGB1

There are three conserved cysteine residues (Cys23, Cys45 and Cys106) on HMGB1 that have been implicated as redox-sensitive regulators of HMGB1’s pro-inflammatory activity. In general, all protein Cys residues with functional thiol groups [containing a sulfur and hydrogen atom (SH)] could be postranslationally modified upon oxidative stress. In silico structural analysis of HMGB1 predicts that Cys23 and Cys45 could reversibly form intramolecular disulfide bonds,18 that can be cleaved by glutaredoxin-catalysed, GSH-dependent reduction. Under severe oxidative stress, Cys-SH groups in proteins can be hyperoxidized to sulfenic [SOH] and then sulfonic acids [SO3H], and such modifications have been shown to promote protein degradation. Whether hyperoxidation of HMGB1 confers its pro-inflammatory function remains unclear. Previous reports have suggested that oxidation-specific epitopes on HMGB1 could be differentially recognized by TLR and RAGE receptors. However, such claims have been found unreliable, and the reports were retracted recently.19–23 Although independent proteomic analyses of HMGB1 support the notion that disulfide bond formation between Cys residues confer HMGB1’s pro-inflammatory functions,24 the overall strength of this body of literatures linking oxidized HMGB1 to pro-inflammatory responses remains low and unconvincing. There remains a critical need to rigorously assess the redox state(s) of HMGB1 in order to (re)-evaluate the signal transduction and biological activities stimulated by HMGB1 that occur under reducing and oxidizing conditions.

In summary, subcellular localization and secretion of HMGB1 direct its biological functions, which is tightly regulated by its post-translational modifications, including phosphorylation,14 acetylation,12 N-linked glycosylation17 and Poly(ADP-Ribosyl)ation.11,16 The regulation of HMGB1 in inflammation and immunity has been systemically reviewed.13 Therefore, the current review will focus on the role of HMGB1 in metabolic diseases, given the fact that inflammation also plays a critical in the initiation, propagation and development of metabolic diseases.25

3 | NUCLEAR FUNCTION OF HMGB1 IN THE REGULATION OF METABOLIC DISEASE

In the nucleus, HMGB1 can bind to or bend with the DNAs or RNAs with its transcriptional partners, and controls gene transcription and affect downstream targets, such as YAP (yes-associated protein (1), HSPB1 (Heat shock protein beta-1) and TNFA. Many of these target genes have previously been associated with metabolic diseases7,26,27 (Figure 2A).

For example, HMGB1 promotes diethylnitrosamine (DEN)-induced liver dysfunctions and tumorigenesis through its impact on...
YAP promoter and increased expression of YAP target genes, such as BIRC5, CCND1, MYC, SPP1 and GPC3. Mechanistically, HMGB1 binds to GABPα, an important transcription regulator of YAP gene expression, and HMGB1-GABPα complex binds to the YAP promoter (Figure 2A). Knockout of HMGB1 reduces cell proliferation but does not cause cell death or DNA damage. Consistently, HMGB1 knockout reduces the expression of core components of the Hippo pathway (e.g., YAP and WWTR1/TAZ) and YAP/TAZ target genes, such as BIRC5, CCND1, MYC, SPP1 and GPC3, independent of Wnt/-catenin and Notch pathways, suggesting that nuclear HMGB1 could affect cell proliferation through regulation of YAP/TAZ expression.

Warburg effect, also known as aerobic glycolysis, is a metabolic hallmark of most cancer cells, including HCC, characterized by an excessive conversion of glucose to lactate, despite sufficient oxygen supply. HMGB1-YAP axis has been shown to be responsible for the Warburg effect in liver tumorigenesis via stabilization of YAP-HIF1α in the nucleus and enhancing HIF1α DNA-binding activity, leading to aerobic glycolysis and Warburg effect (Figure 2A). In addition, HMGB1 regulates the expression of heat shock protein beta-1 (HSPB1), which is essential for maintaining quality control of mitochondria. Mechanistically, HMGB1 increases HSPB1 expression, which controls actin cytoskeleton and delivers damaged mitochondria for degradation by autophagy (i.e., mitophagy). Recent studies have demonstrated HMGB1 as a bona fide RNA-binding protein affecting splicing choices. Together, HMGB1 functions as a DNA- or RNA-binding protein, modulating gene expression, splicing and translation, which are relevant in many pathological conditions. Further studies are warranted to specify which DNA or RNA sequences are bound with HMGB1 and their physiological and disease relevance.

4 | CYTOPLASMIC FUNCTIONS OF HMGB1 IN METABOLIC DISEASES

Cytoplasmic HMGB1 has been shown to associate with proteins involved in mitochondrial metabolism, such as mitochondrial degradation (mitophagy) and quality control, and autophagy. Dysregulation of these processes has been implicated in metabolic diseases. For example, HMGB1 is responsible for the suppressive effects of p53 on autophagy in nonalcoholic fatty liver disease (NAFLD). It has been shown that translocation of HMGB1 from nucleus to cytoplasm, and subsequent induction of Beclin1 expression play important roles in NAFLD. Mechanistically, HMGB1 interacts with Beclin1 and Atg5, which are key components for autophagic initiation and nucleation (Figure 2B). The complex of HMGB1-Beclin1 and HMGB1-Atg5 are resistant to degradation by calpain, inhibiting mitochondria-dependent cell death. As autophagy is a process
underlying many human diseases, it would be interesting to further study the roles of HMGB1 on autophagy in metabolic diseases.

5 | EXTRACELLULAR FUNCTION OF HMGB1 IN METABOLIC DISEASES

Previously, the functions of extracellular HMGB1 in metabolic diseases have been widely studied. Secreted HMGB1 could bind to receptors, such as RAGE, toll-like receptor 2 and 4 (TLR2/4), and CXCR, regulating downstream signalling, including MAPK, PI3K and NF-κB (Figure 2C). All these regulatory events are highly relevant to metabolic diseases, such as diabetes and associated complications, liver diseases (e.g., nonalcoholic steatohepatitis [NASH] and liver injury) and cardiovascular diseases.

HMGB1 is implicated in the development of diabetes and hyperglycemia, and various associated complications in brain, lung, kidney and bones. For example, serum HMGB1 is a predictive biomarker of type 2 diabetes mellitus (T2DM) and chronic obstructive pulmonary disease (COPD). Studies have shown that serum HMGB1 levels are positively correlated with HOMA-IR, fasting plasma glucose (FBG) and glycated haemoglobin (HbA1c), and negatively correlated with lung functions in subjects with both T2DM and COPD. Interestingly, clinical data indicate that the serum HMGB1 levels are not associated with gestational diabetes mellitus (GDM), although HMGB1 was correlated with maternal age, a risk factor of GDM. In addition, HMGB1 plays a critical role in diabetes-related dysfunctions of bone marrow stromal cells (BMSCs) and impaired osteointegration. The regulatory role of secreted HMGB1 in diabetes and associated complications, as well as liver disease and cardiovascular diseases, has been shown to be through its binding to different receptors.

Obstructive sleep apnoea (OSA), a common T2DM complication, leads to exacerbated intermittent hypoxia (IH), which could severely affect cognitive functions. IH induces HMGB1-TLR4 signalling in hippocampal tissue, concomitant with suppressed autophagy and enhanced apoptosis. Silencing of HMGB1 suppressed TLR4 signalling, and restored autophagy and suppressed apoptosis in hippocampal neurons of animal model of T2DM with OSA complication. Activation of microglial cells may account for neuronal apoptosis and cognitive deficits. For example, in one recent study, diabetic KK-Ay mice exhibited increased cognitive dysfunction, microglial activation and hippocampal neuronal apoptosis, compared with C57 control mice. Activation of BV2 microglia leads to active secretion of HMGB1 from microglial cells and the secreted HMGB1 functions as an inflammatory factor and sustains the activation of these microglial cells in a positive feedback loop, leading to deteriorated neuronal damage. Mechanistically, HMGB1 activates NF-κB-p65 in microglia, resulting in the secretion of TNF-α and IL-1β, and excessive ROS, which mediates the apoptosis of HT22 cells via the PI3K/Akt/GSK-3β signalling pathway (Figure 2C). Moreover, extracellular HMGB1 is involved in streptozotocin-induced diabetic nephropathy (DN) via its activation of TLR2, TLR4 and RAGE, while blockade of HMGB1 signalling attenuates streptozotocin-induced DN.

Furthermore, HMGB1 plays a crucial role in diabetic neuropathy accompanied neuroinflammation, characterized by the upregulation of HMGB1 and its receptors (TLR4 and CXCR4) (Figure 2C). In addition, periodontal inflammation in diabetic patients was regulated by HMGB1-RAGE-TNF-α/IL6 signalling. However, the regulation of HMGB1 in inflammatory response and cytokine secretion is context (cell or tissue) dependent. For example, hyperglycaemia-triggered trophoblast cell secretion of IL-8 and anti-inflammatory response is dependent on HMGB1-TLR4 signalling, while IL-1β production was HMGB1-TLR4 signalling independent.

In a high-fat diet (HFD)-induced NAFLD model, HMGB1 expression and extracellular release are potentiated by a saturated fatty acid (palmitic acid) in vitro, whereas the neutralization of endogenous HMGB1 dampens HFD-induced inflammatory responses and impairment of liver functions in vivo. HMGB1 expression is controlled by JNK1/2-ATF2 axis transcriptionally, and the miR-200 family of microRNAs post-transcriptionally. The upregulation and release of HMGB1 could, in turn, self-activate TLR4-JNK1/JNK2-ATF2 signalling, thus forming a positive feedback loop (Figure 2C). Furthermore, clinical studies have revealed that HMGB1 is relevant in colonic inflammation and inflammatory bowel disease (IBD)-like phenotypes with NAFLD. Mechanistically, HMGB1 is secreted from liver in NAFLD, which induces an inflammatory response, through binding to its receptors (RAGE and TLR4), and regulation of redox signalling, leading to ectopic intestinal inflammation. Similarly, previous studies indicated that intestinal epithelial cells (IEC) secrete HMGB1, further elevating enteric inflammation in NAFLD following local injury. Ablation of HMGB1 leads to lipid accumulation in jejunal IEC, decreases chylomicron packaging and/or release, reduces serum triglycerides (TG) and mitigates liver steatosis, thus preventing HMGB1 mice from high-fat, high-cholesterol and fructose-enriched diet (HFCFD) induced-NASH. In the liver tissue of streptozotocin-induced diabetic rats, HMGB1-TLR4 signalling is activated, accompanied by the activation of MAP kinase (p38, ERK, JNK), NFκB-p65 and JAK1/STAT3 signalling pathways, which contributes to systemic inflammation (Figure 2C). Hyperhomocysteinemia (HHcy) induces expression and secretion of HMGB1 in vascular endothelial cells, which is regulated by Neurotrophin-1 (NRP1)-p38 MAPK axis. Vascular endothelial cell inflammation and dysfunction are common complications of diabetes that is controlled by hyperglycaemia-induced miR-106 and subsequent induction of HMGB1 expression and inflammation.

Taken together, extracellular HMGB1 is involved in the development of metabolic diseases, mainly through its cytokine-like effects. Thus, targeting extracellular HMGB1 might provide potential therapeutic agents for metabolic diseases.

6 | PHARMACOLOGICAL INTERVENTIONS OF HMGB1 IN METABOLIC DISEASE

As HMGB1 plays important roles in metabolic diseases, significant efforts have been directed towards the discovery of specific HMGB1 inhibitors and therapies.
mals. Mechanistically, glycyrrhizin inhibits the release of HMGB1, improving mechanical and thermal pain threshold in these ani-
and its receptors (TLR4 and CXCR4) in mice with diabetic neuropa-
tecting the diabetic liver from injury. In addition, another HMGB1-
cade.39 Together, the therapeutic interventions on HMGB1 are
RAGE.54 Hyperglycaemia (HG) exacerbates myocardial ischaemia/
colonic epithelial cells under diabetic state by targeting HMGB1-
ehanced regulatory T cell (Treg) and suppressed IFN-
in line with the reduced infiltration of cells into the pancreatic islets,
presses streptozotocin- induced type 1 diabetes (T1D) development,
JNK), NF-
EP has been shown to mitigate the pro-
inflammatory activity of
HMGB1 under normal physiological and
modifications of HMGB1 and its functions.

8. Yang H, Wang H, Ju Z, et al. MD-2 is required for disulfide HMGB1–
metabolic diseases conditions. Such efforts might lead to the de-
velopment of specific drugs targeting HMGB1-associated metabolic
diseases. Given the critical roles of HMGB1 in maintaining genomic
stability and binding (and bending) to DNAs and RNAs, further studies
are warranted to elucidate more HMGB1 nuclear partners and
their direct target genes in physiological and pathological conditions.

AUTHOR CONTRIBUTIONS
Zhipeng Tao: Conceptualization (equal); investigation (equal); pro-
ject administration (equal); supervision (equal); writing – original
draft (equal); writing – review and editing (equal). Xu Wu: Conceptualization (equal); investigation (equal); project administration (equal); resources (equal); supervision (equal); writing – original
draft (equal); writing – review and editing (equal). Benjamin C.B. Leach: Writing – review and editing (supporting). My N. Helms: Conceptualization (equal); investigation (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

ACKNOWLEDGEMENT
The figures were created with BioRender.com. This work is funded in
part by Melanoma Research Alliance (MRA) postdoctoral fellowship
(812717 to Z. T).

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were gener-
ated or analysed during the current study.

ORCID
Zhipeng Tao https://orcid.org/0000-0002-9582-6950

REFERENCES
1. Nemeth MJ, Kirby MR, Bodine DM. Hmgb3 regulates the balance
between hematopoietic stem cell self-renewal and differentiation. Proc Natl Acad Sci USA. 2006;103(37):13783-13788.
2. Ronfani L, Ferraguti M, Croci L, et al. Reduced fertility and sper-
matogenesis defects in mice lacking chromosomal protein Hmgb2. Development. 2001;128(8):1265-1273.
3. Rouhiainen A, Zhao X, Vanttola P, et al. HMGB4 is expressed by
neuronal cells and affects the expression of genes involved in neu-
ral differentiation. Sci Rep. 2016;6:32960.
4. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein
HMGB1 by necrotic cells triggers inflammation. Nature. 2002;418(6894):191-195.
5. Bianchi ME, Beltrame M. Upwardly mobile proteins. EMBO Rep.
2000;1(2):109-114.
6. Sofiadis K, Nikolic M, Zirkel A, et al. HMGB1 as a rheostat of chro-
matin topology and RNA homeostasis on the path to senescence. bioRxiv. 2019:540146.
7. Gazzar ME, Yoza BK, Chen X, Garcia BA, Young NL, CE MC. Chromatin-specific remodeling by HMGB1 and linker histone H1
silences proinflammatory genes during endotoxin tolerance. Mol Cell Biol. 2009;29(7):1959-1971.
8. Yang H, Wang H, Ju Z, et al. MD-2 is required for disulfide HMGB1-dep-
dendent TLR4 signaling. J Exp Med. 2015;212(1):5-14.

7 | CONCLUSIONS AND PERSPECTIVE
HMGB1 plays multifaced roles in metabolic diseases through its dif-
fferential functions at different subcellular locations. In the nucleus, HMGB1 functions as transcriptional regulator, bending and binding
with DNAs or RNAs. In the cytoplasm, HMGB1 is an autophagy or
mitophagy regulator through its binding to autophagic components.
In the extracellular space, HMGB1 plays distinct roles via its binding
to various receptors and regulates downstream signalling pathways,
which are critical mediators of metabolic diseases. Recently, validity
of studies about redox regulation of HMGB1 has been questioned;
therefore, extra cautions should be exercised to consider the redox
modifications of HMGB1 and its functions.

Since posttranslational regulations of HMGB1 have not been
fully studied, more efforts are needed to explore the posttransla-
tional modifications of HMGB1 under normal physiological and
9. Ito I, Fukazawa J, Yoshida M. Post-translational methylation of high mobility group box 1 (HMGB1) causes its cytoplasmic localization in neutrophils. *J Biol Chem*. 2007;282(22):16336-16344.

10. Bald T, Quast T, Landsberg J, et al. Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. *Nature*. 2014;507(7490):109-113.

11. Yang Z, Li L, Chen L, et al. PARP-1 mediates LPS-induced HMGB1 release by macrophages through regulation of HMGB1 acetylation. *J Immunol*. 2014;193(12):6114-6123.

12. Evankovich J, Cho SW, Zhang R, et al. High mobility group box 1 release from hepatocytes during ischemia and reperfusion injury is mediated by decreased histone deacetylase activity. *J Biol Chem*. 2010;285(51):39888-39897.

13. Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. *Nat Rev Immunol*. 2005;5(5):331-342.

14. Lee H, Park M, Shin N, et al. High mobility group box-1 is phosphorylated by protein kinase C zeta and secreted in colon cancer cells. *Biochem Biophys Res Commun*. 2012;424(2):321-326.

15. Lu B, Antoine DJ, Kwan K, et al. JAK/STAT1 signaling promotes HMGB1 hyperacetylation and nuclear translocation. *Proc Natl Acad Sci*. 2014;111(8):3068-3073.

16. Davis K, Banerjee S, Friggeri A, Bell C, Abraham E, Zerfaoui M. Poly (ADP-ribose) ation of high mobility group box 1 (HMGB1) protein enhances inhibition of effectorcytes. *Mol Med*. 2012;18(3):359-369.

17. Kim YH, Kwak MS, Park JB, et al. N- linked glycosylation plays a crucial role in the secretion of HMGB1. *J Cell Sci*. 2016;129(1):29-38.

18. Hoppe G, Talcott KE, Bhattacharya SK, Crabw JW, Sears JE. Molecular basis for the redox control of nuclear transport of the structural chromatin protein Hmgb1. *Exp Cell Res*. 2006;312(18):3526-3538.

19. Antoine DJ, Jenkins RE, Dear JW, et al. Retraction notice to: molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetyaminophen hepatotoxicity. *J Hepatol*. 2020;73(5):1297.

20. Palmblad K, Schierbeck H, Sundberg E, et al. Retraction notice to: high systemic levels of the cytokine-inducing HMGB1 isofrom secreted in severe macrophage activation syndrome. *Mol Med*. 2020;26(1):131.

21. Sun Q, Loughran P, Shapiro R, et al. Retraction notice: redox-dependent regulation of hepatocyte absent in melanoma 2 inflamasome activation in sterile liver injury in mice. *Hepatology*. 2019;70(1):2244.

22. Walker LE, Frigerio F, Ravizza T, et al. Retraction: molecular isoforms of high-mobility group box 1 are mechanistic biomarkers for epilepsy. *J Clin Invest*. 2019;129(5):2166.

23. Yang H, Lundbäck P, Ottoison L, et al. Retraction note to: redox modification of cysteine residues regulates the cytokine activity of high mobility group box-1 (HMGB1). *Mol Med*. 2020;26(1):133.

24. Venereau E, Casalgrandi M, Schiraldi M, et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. *J Exp Med*. 2012;209(9):1519-1528.

25. Baker RG, Hayden MS, Ghosh S. NF-kB, inflammation, and metabolic disease. *Cell Metab*. 2011;13(3):11-22.

26. Chen R, Zhu S, Fan XG, et al. High mobility group protein B1 controls liver cancer initiation through yes-associated protein-dependent aerobic glycolysis. *Hepatology*. 2018;67(5):1823-1841.

27. Tang D, Kang R, Livesey KM, et al. High-mobility group box 1 is essential for mitochondrial quality control. *Cell Metab*. 2011;13(6):701-711.

28. DeBerardinis RJ, Chandel NS. We need to talk about the Warburg effect. *Nat Metab*. 2020;2(2):127-129.

29. Wal T, Langer T. Mitochondrial dynamics and metabolic regulation. *Trends Endocrinol Metab*. 2016;27(2):105-117.

30. Zhang X, Lin Y, Lin S, et al. Silencing of functional p53 attenuates NAFLD by promoting HMGB1-related autophagy induction. *Hepatol Int*. 2020;14(5):828-841.

31. Behrends C, Sowa ME, Gygi SP, Harper JW. Network organization of the human autophagy system. *Nature*. 2010;466(7302):68-76.

32. Zhu X, Messer JS, Wang Y, et al. Cytosolic HMGB1 controls the cellular autophagy/apoptosis checkpoint during inflammation. *J Clin Invest*. 2015;125(3):1098-1110.

33. Yousefi S, Perozzo R, Schmid I, et al. Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis. *Nat Cell Biol*. 2006;8(10):1124-1132.

34. Yang Y, Klionsky DJ. Autophagy and disease: unanswered questions. *Cell Death Differ*. 2020;27(3):858-871.

35. Thakur V, Sadanandan J, Chattopadhyay M. High-mobility group box 1 protein signaling in painful diabetic neuropathy. *Int J Mol Sci*. 2020;21(3):881.

36. Pawra R, Jalal I. The role of the high-mobility group box 1 protein—toll like receptor pathway in diabetic vascular disease. *J Diabetes Complications*. 2016;30(6):1186-1191.

37. Huang J, Zeng T, Tian Y, et al. Clinical significance of high-mobility group box-1 (HMGB1) in subjects with type 2 diabetes mellitus (T2DM) combined with chronic obstructive pulmonary disease (COPD). *J Clin Lab Anal*. 2019;33(6):e22910.

38. Hill AV, Menon R, Perez-Patron M, Carrillo G, Xu X, Taylor BD. High-mobility group box 1 at the time of parturition in women with gestational diabetes mellitus. *Am J Reprod Immunol*. 2019;82(5):e13175.

39. Liu B, Gan X, Zhao Y, Yu H, Gao J, Yu H. Inhibition of HMGB1 promotes osseointegration under hyperglycemic condition through improvement of BMSC dysfunction. *Oxid Med Cell Longev*. 2019;2019:1-14.

40. Mokhlesi B, Grimaldi D, Becucci G, et al. Effect of one week of 8-hour nightly continuous positive airway pressure treatment of obstructive sleep apnea on glycemic control in type 2 diabetes: a proof-of-concept study. *Am J Respir Crit Care Med*. 2016;194(4):516-519.

41. Guo X, Shi Y, du P, et al. HMGB1/TLR4 promotes apoptosis and reduces autophagy of hippocampal neurons in diabetes combined with OSA. *Life Sci*. 2019;239:117020.

42. Shi Y, Guo X, Zhang J, Zhou H, Sun B, Feng J. DNA binding protein HMGB1 secreted by activated microglia promotes the apoptosis of hippocampal neurons in diabetes complicated with OSA. *Brain Behav Immun*. 2018;73:482-492.

43. Chen X, Ma J, Kwan T, et al. Blockade of HMGB1 attenuates diabetic nephropathy in mice. *Sci Rep*. 2018;8(1):1-13.

44. Akutagawa K, Fujita T, Ouhara K, et al. Glycyrrhizin acid suppresses inflammation and reduces the increased glucose levels induced by the combination of Porphyromonas gulae and ligature placement in diabetic model mice. *Int Immunopharmacol*. 2019;68:30-38.

45. Heim KR, Mulla MJ, Potter JA, Han CS, Guller S, Abrahams VM. Excess glucose induce trophoblast inflammation and limit cell migration through HMGB 1 activation of toll-like receptor 4. *Am J Reprod Immunol*. 2018;80(5):e13044.

46. Chen X, Ling Y, Wei Y, et al. Dual regulation of HMGB1 by combined JNK1/2–ATF2 axis with miR-200 family in nonalcoholic steatohepatitis in mice. *FASEB J*. 2018;32(5):2722-2734.

47. Chao C-Y, Battat R, al Khoury A, Restellini S, Sebastiani G, Bessissow T. Co-existence of non-alcoholic fatty liver disease and inflammatory bowel disease: a review article. *World J Gastroenterol*. 2016;22(34):7727-7734.

48. Chandrashekaran V, Seth RK, Dattaroy D, et al. HMGB1-RAGE pathway drives peroxynitrite signaling-induced IBD-like inflammation in murine nonalcoholic fatty liver disease. *Redox Biol*. 2017;13:8-19.
49. Gaskell H, Ge X, Desert R, et al. Ablation of Hmgb1 in intestinal epithelial cells causes intestinal lipid accumulation and reduces NASH in mice. *Hepatol Commun*. 2020;4(1):92-108.

50. Jovanović Stojanov S, Martinović V, Bogojević D. Modulation of diabetes-related liver injury by the HMGB1/TLR4 inflammatory pathway. *J Physiol Biochem*. 2018;74(2):345-358.

51. Ma Y, Zhang Z, Chen R, et al. NRP1 regulates HMGB1 in vascular endothelial cells under high homocysteine condition. *Am J Physiol Heart Circ Physiol*. 2019;316(5):H1039-H1046.

52. Liu R, Luo Q, You W, Jin M. MicroRNA-106 attenuates hyperglycemia-induced vascular endothelial cell dysfunction by targeting HMGB1. *Gene*. 2018;677:142-148.

53. VanPatten S, Al- Abed Y. High mobility group box-1 (HMGb1): current wisdom and advancement as a potential drug target: miniperpective. *J Med Chem*. 2017;61(12):5093-5107.

54. Wang S-Y, Li JY, Xu JH, et al. Butyrate suppresses abnormal proliferation in colonic epithelial cells under diabetic state by targeting HMGB1. *J Pharmacol Sci*. 2019;139(4):266-274.

55. Soh S, Jun JH, Song JW, Shin EJ, Kwak YL, Shim JK. Ethyl pyruvate attenuates myocardial ischemia-reperfusion injury exacerbated by hyperglycemia via retained inhibitory effect on HMGB1. *Int J Cardiol*. 2018;252:156-162.

56. Koprivica I, Vujčičić M, Gajić D, Saksida T, Stojanović I. Ethyl pyruvate stimulates regulatory T cells and ameliorates type 1 diabetes development in mice. *Front Immunol*. 2019;9:3130.

**How to cite this article:** Tao Z, Helms MN, Leach BCB, Wu X. Molecular insights into the multifaceted functions and therapeutic targeting of high mobility group box 1 in metabolic diseases. *J Cell Mol Med*. 2022;26:3809-3815. doi: [10.1111/jcmm.17448](https://doi.org/10.1111/jcmm.17448)