State of the art paper

The role of HMGB1 in gastrointestinal cancers

Nimet Yılmaz[1], Mustafa Yıldırım[2], Hanım Seval Savaş[3], Hülya Çiçek[3], Özlem Nuray Sever[4]

[1]Department of Gastroenterology, Sanko University, Gaziantep, Turkey
[2]Department of Oncology, School of Medicine, Sanko University, Gaziantep, Turkey
[3]Department of Medical Biochemistry, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[4]Department of Oncology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

Corresponding author:
Nimet Yılmaz
Department of Gastroenterology
Sanko University
Gaziantep, Turkey
Phone: 05336690001
E-mail: drnimet23@hotmail.com

Submitted: 26 January 2021
Accepted: 21 March 2021

Arch Med Sci Civil Dis 2021; 6: e1–e7
DOI: https://doi.org/10.5114/amscd.2021.105385

Abstract

Despite advances in diagnostic and therapeutic methods, gastrointestinal (GI) cancers have both a high incidence and a high mortality rate. In addition to surgery, chemotherapy and radiotherapy, novel modalities such as immunotherapy are increasingly used in the treatment of these cancers. However, the prognosis in GI cancers remains poor despite the availability of these treatments, which prompted the search for new prognostic and predictive markers. High-mobility group box-1 (HMGB1) is a non-histone DNA protein which is known as a nuclear transcription factor. The search for new therapeutic targets has also gained importance. In this review, the prognostic and predictive role of HMGB1 in gastrointestinal cancers will be discussed in light of current literature.

Key words: gastrointestinal cancers, HMGB1, predictive markers, prognostic markers.

Introduction

Despite advances in diagnostic and therapeutic methods, gastrointestinal (GI) cancers have both a high incidence and a high mortality rate. In addition to surgery, chemotherapy and radiotherapy, novel modalities such as immunotherapy are increasingly used in the treatment of these cancers [1]. However, the prognosis in GI cancers remains poor despite the availability of these treatments, which prompted the search for new prognostic and predictive markers. The search for new therapeutic targets has also gained importance. In this review, the prognostic and predictive role of high-mobility group box-1 (HMGB1) in gastrointestinal cancers will be discussed in light of current literature.

High-mobility group (HMG) proteins

High-mobility group (HMG) proteins were first purified from the cell nuclei of calf thymus as a group of proteins with high electrophoretic mobility in 1973 and are named after their fast migration in gel electrophoresis. HMG proteins consist of three superfamilies: HMGA, high-mobility group box (HMGB) and HMGN proteins. The HMGB protein family comprises three groups designated as HMGB1, HMGB2 and HMGB3. While the expression of HMGB3 and HMGB2 is limited, HMGB1 is widely expressed [2].

HMGB1 is a non-histone DNA protein which is known as a nuclear transcription factor. Structurally, HMGB1 protein is a highly conserved protein of 215 amino acids with two DNA binding domains (Box-A and Box-B) and a negatively charged C-terminal region. Although HMGB1 was initially considered to be a nuclear protein involved in regulating the transcription level of various genes, recent studies have demonstrated its further role as a cytokine that triggers the development of inflammation-related diseases including cancer by increasing the expression of other inflammatory cytokines. Inside the nucleus, HMGB1 interacts with DNA and histones to determine chromatin structure and regulates basic processes such as transcription. Outside the cell, HMGB1 assumes a new identity to act as a danger signal or damage-associated molecular pattern (DAMP) [3, 4].

HMGB1 is passively secreted from necrotic cells and actively released from inflammatory cells and has a high binding affinity for some receptors. The receptor for advanced glycation end products (RAGE) and Toll-like receptors (TLR)-2, TLR-4 and TLR-9 are some of these receptors [5]. RAGE is the receptor for extracellular HMGB1 that mediates its intracellular action. This way, HMGB1 acts as an extracellular signaling molecule in inflammation, cell differentiation, cell migration and tumor metastasis. HMGB1 protein and its receptor RAGE are defined as a ligand-receptor pair that has a pivotal role in the proliferation of tumor cells [6].

HMGB1 protein and cancer

HMGB1 protein is found in the nucleus of both cancer cells and normal cells, and overexpression of HMGB1 has been demonstrated in many types of cancer including hepatocellular cancer, prostate cancer, gastrointestinal cancers and breast cancer [7–9]. Moreover, there are studies suggesting that HMGB1 can be used as a marker protein in predicting the prognosis of tumor stages in different cancers [10–12]. When released from damaged or cancerous cells, HMGB1 activates mitogen-activated protein kinases (MAPKs) by binding to a number of specific receptors and enhances phagocytosis.

As a transcription factor, HMGB1 binds to the promoter region either alone or with the help of other transcription factors already bound to DNA and thereby regulates the expression of respective genes. Once released from damaged cells, HMGB1 binds to the DNA of the cell and this HMGB1-DNA complex then activates the TLR-9 signaling pathway that leads to tumor formation. Acetylation of HMGB1 weakens its binding to DNA and accelerates its migration to different tissues, resulting in secretion of inflammatory cytokines [2, 13]. Consequently, normal immune cells are activated to secrete different types of inflammatory cytokines to create a microenvironment that favors growth and propagation of cancer. HMGB1 is transported to the extracellular space and sends alarm signals to warn the innate immune system in response to stress or uncontrolled cell death. This action is believed to be mediated by active transport of HMB1 from inflammatory cells such as macrophages or passive release from necrotic cells during tissue damage and oxidative stress. HMGB1 has been shown to be released in the extracellular milieu during tumor growth, angiogenesis and metastasis stages [6, 14–16].

There are no adequate studies on the intracellular localization of HMGB1 in malignant tumors. In one study, intracellular localization of HMGB1 was demonstrated to be associated with histologic differentiation of malignant tumors. The authors of that study reported that moderately differentiated carcinomas exhibited a perinuclear localization of the protein, whereas a tendency for non-specific nuclear localization was found in poorly differentiated carcinomas [6].

The biological function of HMGB1 varies depending on its intracellular location and expression. Accordingly, HMGB1 can play paradoxical roles in promoting or suppressing cancer during the progression of malignant tumors. Inside the nucleus, HMGB1 is a highly conserved chromosomal protein engaged in DNA repair, transcription, replication as well as genome stability. Post-translational modifications including phosphorylation, acetylation and methylation allow translocation of HMGB1 to the cytoplasm, thereby promoting cell proliferation, autophagy and inflammation. HMGB1 secreted to extracellular medium plays a role in the progression of cancer through the RAGE receptor [6].

In several studies, increased HMGB1 level was shown to block aerobic respiration by inhibiting the enzyme pyruvate kinase isoform M2 and to cause a metabolic shift from aerobic to anaerobic respiration by choosing an alternative energy pathway of glutaminolysis. It was suggested that inhibition of the alternative energy producing pathway of glutaminolysis in HMGB1-dependent tumor cells may offer a beneficial therapeutic strategy for prevention and treatment of cancer. Even under hypoxic conditions, solid tumors continue to grow and malignant cells may survive and proliferate. Hypoxia induces expression of hypoxia inducible factor-1 (HIF-1), which promotes the translocation of HMGB1 from the nucleus to the cytoplasm, and proliferative ability of solid tumors has been associated with hypoxia. It is known that HMGB1 is a protein involved in tumor progression and contributes to an increase in tumor tissue due to its angiogenic effect. While HMGB1 mediates cancer cell growth via mitogen-activated protein

kinases, it promotes cancer cell invasion through RAGE [17].

Binding of HMGB1 to the RAGE receptor activates the oncogene Ras, which then activates the MAP kinase-mediated nuclear factor κB (NF-κB) inflammatory pathway. NF-κB is a transcription factor involved in the regulation of immune responses, cell proliferation and apoptosis. Overexpression of NF-κB promotes COX-2 expression and COX-2 induces necrotic cell death, which results in the release of HMGB1. Additionally, activated NF-κB induces expression of proinflammatory cytokines such as IL-1β, IL-6, IL-18 and TNF-α, which are responsible for inflammation and cancer development. Then, these cytokines activate macrophages and dendritic cells to release HMGB1 into the extracellular environment. Furthermore, dendritic cell-derived T-cell immunoglobulin domain and mucin domain-3 (TIM-3) was shown to interact with HMGB1 and interfere with the transport of nucleic acids into endosomal vesicles, resulting in impaired antitumor effectiveness of DNA vaccines and cytotoxic chemotherapy. This suggests that HMGB1 may contribute to the development of resistance to treatment by interacting with other cytokines that carry chemical signals between cells [18–22].

HMGB1 protein and colorectal cancer

Colorectal cancer (CRC) is among the most common cancers worldwide and the fourth leading cause of cancer-related deaths. CRC develops as a result of neoplastic transformation from adenomas to adenocarcinomas. This malignant transformation can be triggered by both genetic and epigenetic factors, and complete transformation can occur over decades, providing the opportunity for early diagnosis [23].

Tumor formation is defined by the balance between autophagy and apoptosis. p53 plays a transcription-dependent or -independent role in apoptosis, autophagy and the cell cycle. Overexpression of p53 and HMGB1 has been demonstrated in tumor tissues of CRC patients compared to normal colorectal mucosa. Both HMGB1 and p53 are associated with most of the hallmarks that define the altered biology of cancer and are closely linked with the development of cancer. The balance between apoptosis and autophagy is regulated by the p53/HMGB1 complex. It was shown in CRC patients that increased cytosolic HMGB1 promotes autophagy and increased p53 enhances apoptosis in colon cancer cells [24]. Nuclear localization of p53 and HMGB1 in tumors from patients with colon adenocarcinoma showed a positive correlation with survival time from the diagnosis. Therefore, HMGB1 and p53 are crucial for colon cancer biology and have a critical role in the cross-regulation of apoptosis and autophagy [25].

HMGB1 can inhibit apoptosis through different pathways. Overexpression of HMGB1 inhibits important apoptotic steps by suppressing the activity of caspase-3 and caspase-9. HMGB1 overexpression was shown to regulate cytochrome-apoptosis inhibitor protein 2 (c-IAP2), an antiapoptotic protein. In CRC, c-IAP2 levels were found to be directly correlated with HMGB1 expression [26]. However, HMGB1 was also shown to inhibit the expression of BAK, which is a member of the proapoptotic Bcl-2 family [27].

Studies have shown that HMGB1 overexpression plays a key role in cell migration, tumor progression and metastasis in CRC, and therefore it may be considered as a significant predictive factor. However, the HMGB1 gene silencing approach slowed down tumor growth, invasion and metastasis in CRC. Thus, it is considered that HMGB1 may be a prognostic factor and could affect the expression of other genes involved in cell growth, apoptosis, invasion and metastasis [28–30].

In the pathogenesis of CRC, the role of HMGB1 depends on the redox state of the protein. There are studies on the subcellular localization of HMGB1 in CRC, but its clinical, pathological and prognostic significance remains unclear because these studies involved only a small number of CRC tissue samples [31, 32]. In a recent study, nuclear HMGB1 expression was found to be generally positive in normal colorectal, colorectal adenoma and CRC tissue specimens. Moreover, the rates of strongly positive nuclear HMGB1 expression were significantly greater in colorectal adenoma and CRC tissue specimens than in normal colorectal tissue specimens, whereas the rate was slightly higher in colorectal adenoma tissues than in CRC tissues. Based on these findings, the authors of that study suggested that increased nuclear HMGB1 expression occurs in the early stage of colorectal neoplastic lesions [33]. Similarly, Volp *et al.* reported significantly increased levels of HMGB1 expression in colon carcinoma compared to non-cancerous colon mucosa [34].

Yao *et al.* observed that increased HMGB1 expression correlated with poor overall survival in CRC patients and suggested that HMGB1 protein may be a valuable biomarker to monitor disease progression in CRC patients [35].

In a recent study by Huang *et al.*, significant increases were found in the expression of the translationally controlled tumor protein (TCTP) in CRC tissue and the serum HMGB1 concentration in CRC patients, and a strong positive correlation between them was reported. Also, TCTP expression and HMGB1 concentration were substantially higher in the samples from CRC patients with distant metastasis, indicating that they are correlated with the clinical severity and prognosis of

CRC. Their study suggested that TCTP promotes CRC metastasis by regulating the expression and release of HMGB1 and the activation of the NF-κB signaling pathway [36]. Consistently, previous studies have also shown that HMGB1 and TCTP may induce epithelial-mesenchymal transition and thus enhance metastasis and invasion [37, 38]. TCTP expression is frequently increased in cancer, and TCTP overexpression has been associated with poor prognosis in many cancers including hepatocellular and colorectal cancer [39]. Lee *et al.* reported that for patients with stage I CRC, the diagnostic accuracy of serum HMGB1 was markedly greater than that of carcinoembryonic antigen (CEA), which is the most commonly used serum marker in the early diagnosis of CRC [40]. Another study in Chinese CRC patients reported that patients with positive HMGB1 expression had a significantly worse 5-year survival rate compared to patients with negative expression (73.3% vs. 82.1%, $p = 0.031$) [41]. Collectively, these studies have demonstrated that HMGB1 is a key factor involved in the growth, progression, angiogenesis, invasion and metastasis of CRC. Therefore, HMGB1 might be a promising biomarker in predicting clinical outcomes in CRC patients.

HMGB1 protein and gastric cancer

HMGB1 is highly expressed in cancer tissues and closely linked with apoptosis, proliferation and migration of cancer cells. In gastric cancer, a decreased grade of tumor differentiation and increased depth of invasion were observed in the presence of HMGB1 expression, which was associated with higher stage. These findings suggest that HMGB1 is an independent prognostic factor for gastric cancer [42]. High HMGB1 expression was observed in gastric cancer cells and its receptor RAGE was found to be closely correlated with invasion and metastasis of gastric cancer [12].

In one study, Zhang *et al.* found that increased HMGB1 expression promoted cell proliferation and tumor metastasis in gastric adenocarcinoma and knockdown of HMGB1 caused suppression of growth and metastasis of gastric adenocarcinoma cells via the NF-κB pathway *in vitro* and *in vivo* [43].

It is known that autophagy-related release of HMGB1 protects cancer cells from a number of chemotherapeutic agents. In one study, extracellular HMGB1 was found to protect gastric cancer cells from apoptosis induced by vincristine, a drug targeting microtubules, through transcriptional upregulation of Mcl-1. The effect of extracellular HMGB1 on transcriptional regulation of Mcl-1 was confirmed in gastric cancer cells treated with recombinant HMGB1 [44].

Previously, a significant inhibitory effect of silencing of HMGB1 expression on the metastatic abilities of MGC-803 gastric cancer cells was demonstrated [45]. In a separate study, HMGB1 silencing also led to sensitization of the cells to oxaliplatin and induced apoptosis in MGC-803 cells [46]. Therefore, HMGB1 plays an essential role in the proliferation and metastasis of MGC-803 cells and represents a potential target for therapeutic interventions directed at gastric cancer.

Aloin, a bioactive compound extracted from *Aloe vera*, has anti-tumor activity and has been shown to induce apoptosis by regulating activation of the MAPK signaling pathway in gastric cancer cells [47]. A recent study investigated the role of HMGB1 in apoptosis induced by aloin in gastric cancer cells. The authors of the study concluded that aloin induces apoptosis in gastric cancer cells by reducing the expression and release of HMGB1 [48].

HMGB1 protein and pancreatic cancer

Studies have shown that RAGE activation via its ligands promotes pancreatic tumor growth by stimulating both cell proliferation and migration. Tumor cells have an increased demand for adenosine triphosphate (ATP) to sustain anabolism and proliferation. RAGE is present in the mitochondria of cultured tumor cells and primary tumors. RAGE and HMGB1 are required for optimal mitochondrial function within tumors. RAGE and HMGB1 enhance tumor cell mitochondrial complex I activity, ATP production, tumor cell proliferation and migration in a coordinated manner. In one study, lower HMGB1 expression was found in normal pancreatic tissues than in cancerous pancreatic tissues [49]. In Kang *et al.*'s study, lack of RAGE or inhibition of HMGB1 release was shown to decrease ATP production and slow down the growth of pancreatic cancer cells *in vitro* and *in vivo* [50]. Targeted knockdown of RAGE in the tumor cell results in increased apoptosis, diminished autophagy and reduced tumor cell survival. However, overexpression of RAGE is associated with enhanced autophagy, diminished apoptosis and greater tumor cell viability. RAGE limits apoptosis via a p53-dependent mitochondrial pathway.

A recent study examined the effect of RAGE upregulation on proliferation and migration of the human pancreatic cancer Panc-1 cell line and showed that moderate RAGE expression of RAGE in Panc-1 cells caused an increase in cell proliferation but a reduction in cell migration [51].

Pancreatic ductal cell adenocarcinoma (PDAC) driven by oncogenic K-Ras is still among the deadliest cancers. One study demonstrated that HMGB1 remarkably suppresses oncogenic K-Ras-driven pancreatic tumor formation by inhibiting proinflammatory nucleosome release mediated by chromosome instability [52]. Conditional genetic ablation of either single or both alleles of

HMGB1 in the pancreas rendered mice extremely sensitive to oncogenic K-Ras-driven initiation of precursor lesions at birth, including pancreatic intraepithelial neoplasms. It is now known that loss of HMGB1 in the pancreas causes oxidative damage and chromosome instability, leading to inflammatory nucleosome release and enhanced pancreatic tumorigenesis driven by K-Ras. Pharmacological inhibition of intracellular HMGB1 loss limits K-Ras-driven tumor formation in mice, suggesting that HMGB1 is a tumor suppressor in PDAC. In the same study, HMGB1 loss caused abnormal telomeres and nucleosome release in PDAC cells. Conditional inhibition of HMGB1 in the pancreas leads to a marked acceleration of K-Ras-driven carcinogenesis and this process requires activation of RAGE, a DAMP receptor. Thus, the impaired HMGB1-nucleosome-RAGE-mediated DAMP pathway contributes to activation of K-Ras signaling and may represent a promising therapeutic target for PDAC [52].

In a study investigating the diagnostic and prognostic value of serum HMGB1 in PDAC, serum HMGB1 was correlated with the presence and advanced stage of PDAC, and the sensitivity and specificity of HMGB1 were superior to CA19-9 and CEA. The authors of that study found that PDAC patients with high serum HMGB1 values (> 30 ng/ml) had a worse prognosis than PDAC patients with low HMGB1 values (≤ 30 ng/ml). These data suggest that serum HMGB1 is a superior diagnostic and prognostic biomarker for PDAC compared to CA19-9 and CEA, which are commonly used biomarkers for PDAC [11].

HMGB1 protein and liver cancer

Several studies have shown that there are strong correlations between serum HMGB1 and pathological symptoms of liver cancer and p53 induces HMGB1 expression in hepatocellular carcinoma (HCC) cells [7, 53]. In a study exploring the expression of HMGB1 and its clinical relevance in human primary liver cancer, HMGB1 was found to be highly expressed in liver cancer in comparison to normal tissues and was positively correlated with the pathological grade and distant metastases of liver cancer. These results suggest that HMGB1 may be used as a marker to predict prognosis and tumor stages in HCC [54].

HMGB1 was shown to promote invasion and metastasis in HCC through a process dependent on caspase-1 activation and subsequent activation of both TLR-4 and RAGE pathways. The same study also demonstrated that HMGB1 overexpression or treatment with recombinant HMGB1 promoted the invasiveness of HCC cells but knockdown of HMGB1 considerably reduced HCC invasion [55]. In another study, inhibition of HMGB1 was shown to enhance hepatoma cell apoptosis induced by doxorubicin [56].

In Xiao *et al.*'s study, HMGB1 protein was found to be much more strongly expressed in almost all HCCs than in normal liver and cirrhotic liver tissues. The same study also showed significantly worse overall survival in patients with high HMGB1 expression compared to those with low expression. The authors suggested that HMGB1 expression may be a novel, independent predictor for HCC patients [57].

In conclusion, HMGB1 is an important prognostic factor for gastrointestinal cancers due to its role in angiogenesis, metastasis and inflammations. Treatments targeting HMGB1 seem promising in these patient populations with poor prognosis.

Conflict of interest

The authors declare no conflict of interest.

References

1. Güthle M, Ettrich T, Seufferlein T. Immunotherapy in gastrointestinal cancers. Visc Med 2020; 36: 231-37.
2. Zhang J, McCauley MJ, Maher LJ 3rd, Williams MC, Israeloff NE. Mechanism of DNA flexibility enhancement by HMGB proteins. Nucleic Acids Res 2009; 37: 1107-14.
3. Bustin M, Lehn DA, Landsman D. Structural features of the HMG chromosomal proteins and their genes. Biochim Biophys Acta 1990; 1049: 231-43.
4. Alexandrova EA, Beltchev BG. Acetylated HMG1 protein interacts specifically with homologous DNA polymerase alpha in vitro. Biochem Biophys Res Commun 1988; 154: 918-27.
5. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 2002; 418: 191-5.
6. Kostova N, Zlateva S, Ugrinova I, Pasheva E. The expression of HMGB1 protein and its receptor RAGE in human malignant tumors. Mol Cell Biochem 2010; 337: 251-8.
7. Yan HX, Wu HP, Zhang HL, et al. p53 promotes inflammation-associated hepatocarcinogenesis by inducing HMGB1 release. J Hepatol 2013; 59: 762-8.
8. Gnanasekar M, Thirugnanam S, Ramaswamy K. Short hairpin RNA (shRNA) constructs targeting high mobility group box-1 (HMGB1) expression leads to inhibition of prostate cancer cell survival and apoptosis. Int J Oncol 2009; 34: 425-31.
9. Jiao Y, Wang HC, Fan SJ. Growth suppression and radiosensitivity increase by HMGB1 in breast cancer. Acta Pharmacol Sin 2007; 28: 1957-67.
10. Zhang X, Yu J, Li M, Zhu H, Sun X, Kong L. The association of HMGB1 expression with clinicopathological significance and prognosis in Asian patients with colorectal carcinoma: a meta-analysis and literature review. Onco Targets Ther 2016; 9: 4901-11.
11. Chung HW, Lim JB, Jang S, Lee KJ, Park KH, Song SY. Serum high mobility group box-1 is a powerful diagnostic and prognostic biomarker for pancreatic ductal adenocarcinoma. Cancer Sci 2012; 103: 1714-21.
12. Kuniyasu H, Oue N, Wakikawa A, et al. Expression of receptors for advanced glycation end-products (RAGE)

is closely associated with the invasive and metastatic activity of gastric cancer. J Pathol 2002; 196: 163-70.
13. Thomas JO, Travers AA. HMG1 and 2, and related 'architectural' DNA binding proteins. Trends Biochem Sci 2001; 26: 167-74.
14. Stros M, Ozaki T, Bacikova A, Kageyama H, Nakagawara A. HMGB1 and HMGB2 cell-specifically down-regulate the p53- and p73- dependent sequence-specific transactivation from the human Bax gene promoter. J Biol Chem 2002; 277: 7157-64.
15. Qin S, Wang H, Yuan R, et al. Role of HMGB1 in apoptosis-mediated sepsis lethality. J Exp Med 2006; 203: 1637-42.
16. Campana L, Bosurgi L, Rovere-Querini P. HMGB1: a two-headed signal regulating tumor progression and immunity. Curr Opin Immunol 2008; 20: 518-23.
17. Gdynia G, Sauer SW, Kopitz J, et al. The HMGB1 protein induces a metabolic type of tumour cell death by blocking aerobic respiration. Nat Commun 2016; 7: 10764.
18. Kawanishi S, Ohnishi S, Ma N, Hiraku Y, Murata M. Crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. Int J Mol Sci 2017; 18: 1808.
19. Pistoia V, Pezzolo A. Involvement of HMGB1 in resistance to tumor vessel-targeted, monoclonal antibody-based immunotherapy. J Immunol Res 2016; 2016: 3142365.
20. Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol 2010; 28:367-88.
21. Yang H, Wang H, Czura CJ, Tracey KJ. The cytokine activity of HMGB1. J Leukoc Biol 2005; 78: 1-8.
22. Yang H, Hreggvidsdottir HS, Palmblad K, et al. A critical cysteine is required for HMGB1 binding to Toll-like receptor 4 and activation of macrophage cytokine release. Proc Natl Acad Sci USA 2010; 107: 11942-7.
23. Fearon ER, Vogelstein B. A genetic model for colorectal tumourigenesis. Cell 1990; 61: 759-67.
24. Faham A, Bennett D, Altin JG. Liposomal Ag engrafted with peptides of sequence derived from HMGB1 induce potent Ag-specific and anti-tumour immunity. Vaccine 2009; 27: 5846-54.
25. Livesey KM, Kang R, Zeh HJ 3rd, Lotze MT, Tang D. Direct molecular interactions between HMGB1 and TP53 in colorectal cancer. Autophagy 2012; 8: 846-8.
26. He Q, Liang CH, Lippard SJ. Steroid hormones induce HMG1 overexpression and sensitize breast cancer cells to cisplatin and carboplatin. Proc Natl Acad Sci USA 2000; 97: 5768-72.
27. Barnes KR, Kutikov A, Lippard SJ. Synthesis, characterization, and cytotoxicity of a series of estrogen-tethered platinum(IV) complexes. Chem Biol 2004; 11: 557-64.
28. Zhang Z, Wang M, Zhou L, et al. Increased HMGB1 and cleaved caspase-3 stimulate the proliferation of tumour cells and are correlated with the poor prognosis in colorectal cancer. J Exp Clin Cancer Res 2015; 34: 51.
29. He S, Cheng J, Sun L, et al. HMGB1 released by irradiated tumor cells promotes living tumor cell proliferation via paracrine effect. Cell Death Dis 2018; 9: 648.
30. Li Z, Wang H, Song B, Sun Y, Xu Z, Han J. Silencing HMGB1 expression by lentivirus-mediated small interfering RNA (siRNA) inhibits the proliferation and invasion of colorectal cancer LoVo cells in-vitro and in-vivo. Zhonghua Zhong Liu Za Zhi 2015; 37: 664-70.
31. Peng RQ, Wu XJ, Ding Y, et al. Co-expression of nuclear and cytoplasmic HMGB1 is inversely associated with infiltration of CD45RO+ T cells and prognosis in patients with stage IIIB colon cancer. BMC Cancer 2010; 10: 496.
32. Li Z, Wang H, Song B, et al. Expression of high mobility group box-1 in colorectal cancer and its clinical significance. Chin J Gastrointest Surg 2015; 18: 616-9.
33. Wang CQ, Huang BF, Wang Y, et al. Subcellular localization of HMGB1 in colorectal cancer impacts on tumor grade and survival prognosis. Sci Rep 2020; 10: 18587.
34. Volp K, Brezniceanu ML, Bosser S, et al. Increased expression of high mobility group box 1 (HMGB1) is associated with an elevated level of the antiapoptotic c-IAP2 protein in human colon carcinomas. Gut 2006; 55: 234-42.
35. Yao X, Zhao G, Yang H, Hong X, Bie L, Liu G. Overexpression of high-mobility group box-1 correlates with tumor progression and poor prognosis in human colorectal carcinoma. J Cancer Res Clin Oncol 2010; 136: 677-84.
36. Huang M, Geng Y, Deng Q, et al. Translationally controlled tumor protein affects colorectal cancer metastasis through the high mobility group box 1-dependent pathway. Int J Oncol 2018; 53: 1481-92.
37. Zhu L, Li X, Chen Y, Fang J, Ge Z. High-mobility group box 1: a novel inducer of the epithelial-mesenchymal transition in colorectal carcinoma. Cancer Lett 2015; 357: 527-34.
38. Sharma S, Evans A, Hemers E. Mesenchymal-epithelial signalling in tumour microenvironment: role of high-mobility group box 1. Cell Tissue Res 2016; 365: 357-66.
39. Xiao B, Chen D, Luo S, et al. Extracellular translationally controlled tumor protein promotes colorectal cancer invasion and metastasis through Cdc42/JNK/MMP9 signaling. Oncotarget 2016; 7: 50057-73.
40. Lee H, Song M, Shin N, et al. Diagnostic significance of serum HMGB1 in colorectal carcinomas. PLoS One 2012; 7: 34318.
41. Liu DB. Prognostic research of transgelin, MMP-7 and HMGB1 Protein Expression in Rectal cancer [graduation thesis]. An Hui Medical University 2013.
42. Suren D, Arda Gokay A, Sayiner A. High mobility group box 1 (HMGB1) expression in gastric adenocarcinomas. J BUON 2018; 23: 422-7.
43. Zhang J, Kou YB, Zhu JS, Chen WX, Li S. Knockdown of HMGB1 inhibits growth and invasion of gastric cancer cells through the NF-κB pathway in vitro and in vivo. Int J Oncol 2014; 44: 1268-76.
44. Zhan Z, Li Q, Wu P, et al. Autophagy-mediated HMGB1 release antagonizes apoptosis of gastric cancer cells induced by vincristine via transcriptional regulation of Mcl-1. Autophagy 2012; 8: 109-21.
45. Li ZJ, Song B, Liu J, et al. Inhibitory effect of silencing of HMGB1 gene expression on the invasive and metastatic abilities of MGC-803 gastric cancer cells. Zhonghua Zhong Liu Za Zhi 2013; 35: 244-8.
46. Song B, Song WG, Li ZJ, et al. Effect of HMGB1 silencing on cell proliferation, invasion and apoptosis of MGC-803 gastric cancer cells. Cell Biochem Funct 2012; 30: 11-7.
47. Wang ZQ, Tao H, Ma YF, et al. Aloin induces apoptosis via regulating the activation of MAPKs signaling pathway in human gastric cancer cells in vitro. Nan Fang Yi Ke Da Xue Xue Bao 2018; 38: 1025-31.
48. Tao H, Tang T, Wang S, et al. The molecular mechanisms of Aloin induce gastric cancer cells apoptosis by targeting high mobility group box 1. Drug Design Develop Ther 2019; 13: 1221-31.
49. Takeda T, Izumi H, Kitada S, et al. The combination of a nuclear HMGB1-positive and HMGB2-negative expression is potentially associated with a shortened survival in patients with pancreatic ductal adenocarcinoma. Tumour Biol 2014; 35: 10555-69.

50. Kang R, Tang D, Schapiro NE, et al. The HMGB1/RAGE inflammatory pathway promotes pancreatic tumor growth by regulating mitochondrial bioenergetics. Oncogene 2014; 33: 567-77.
51. Swami P, Thiyagarajan S, Vidger A, et al. RAGE up-regulation differently affects cell proliferation and migration in pancreatic cancer cells. Int J Mol Sci 2020; 21: 7723.
52. Kang R, Xie Y, Zhang Q, et al. Intracellular HMGB1 as a novel tumor suppressor of pancreatic cancer. Cell Res 2017; 27: 916-32.
53. Kamo N, Ke B, Ghaffari AA, Busuttil RW, Cheng G, Kupiec-Weglinski JW. ASC/caspase-1/IL-1beta signaling triggers inflammatory responses by promoting HMGB1 induction in liver ischemia/reperfusion injury. Hepatology 2013; 58: 351-62.
54. Dong YD, Cui L, Peng CH, Cheng DF, Han BS, Huang F. Expression and clinical significance of HMGB1 in human liver cancer: knockdown inhibits tumour growth and metastasisin vitro and in vivo. Oncol Rep 2013; 29: 87-94.
55. Yan W, Chang Y, Liang X, et al. High-mobility group box 1 activates caspase-1 and promotes hepatocellular carcinoma invasiveness and metastases. Hepatology 2012; 55: 1863-75.
56. Lu L, Zhang D, Xu Y, Bai G, Lv Y, Liang J. miR-505 enhances doxorubicin-induced cytotoxicity in hepatocellular carcinoma through repressing the Akt pathway by directly targeting HMGB1. Biomed Pharmacother 2018; 104: 613-21.
57. Xiao J, Ding Y, Huang J, et al. The association of HMGB1 gene with the prognosis of HCC. PLoS One 2014; 9: 89097.