The function and mechanism of HMGB1 in lung cancer and its potential therapeutic implications (Review)

LEI WU[1-3] and LILI YANG[1-3]

[1]Department of Immunology, Tianjin Cancer Institute and Hospital, Tianjin Medical University; [2]National Clinical Research Center of Cancer; [3]Key Laboratory of Cancer Immunology and Biotherapy, Tianjin Cancer Institute and Hospital, Tianjin Medical University, Tianjin 300060, P.R. China

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Abstract. As a non-histone chromatin-associated protein, high-mobility group box-1 (HMGB1) performs a pivotal function in various human diseases, including autoimmune diseases, neurodegenerative diseases and cancer. Overexpression of HMGB1 has been demonstrated in numerous types of cancer, including breast cancer, colorectal cancer, lung cancer and hepatocellular carcinoma. However, the underlying mechanism of HMGB1 function in lung cancer remains to be elucidated. The present study aimed to analyze, and summarize the role and mechanism of HMGB1 in lung cancer by retrieving available literature regarding HMGB1 in association with lung cancer. It provides comprehensive information on the association of HMGB1 with the carcinogenesis and progression of lung cancer, and discusses the molecular mechanism of these processes. HMGB1 may induce tumorigenesis, metastasis and chemotherapy resistance in lung cancer. Overall, it is evident that HMGB1 serves an important role in the development and progression of lung cancer, and this review warrants further investigation into HMGB1 as a novel target for cancer therapy.

Contents

Correspondence to: Dr Lili Yang, Department of Immunology, Tianjin Cancer Institute and Hospital, Tianjin Medical University, Huanhuxi Road, Tiyuanbei, Hexi, Tianjin 300060, P.R. China
E-mail: yanglili@tjmuch.com

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1. Introduction

Lung cancer has a high prevalence worldwide, and is associated with the highest morbidity and mortality rates among all types of malignant tumor (1). Small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), develop and metastasize differently, and are the two groups of lung cancer (2). Lung cancer tumors are commonly treated through surgery, chemotherapy, radiation therapy or targeted drug therapy. However, lung cancer is usually detected at the advanced stage, and, in severe cases, cancer cells may have already metastasized to other organs (3). Therefore, the identification of biomarkers to allow for early detection, diagnosis and therapeutic targeting of lung cancer is required.

High-mobility group box 1 (HMGB1), a member of the high-mobility group protein superfamily, is widely expressed and highly abundant (4,5). HMGB1 is secretively and intracellularly active, and serves important roles in biological and pathological processes (4,6,7). HMGB1 exists in the nucleus, and acts as an architectural chromatin-binding factor by binding DNA, thus maintaining the structure and stability of chromosomes (8). HMGB1 also translocates to the cytoplasm, where it activates autophagy by binding to beclin1 (9). Secretive HMGB1 is actively secreted by immune cells, and passively released during cell death and cell injury (8,10,11). It serves as an extracellular signaling molecule and damage-associated molecular pattern molecule (12). Once released, soluble HMGB1 binds to several cell surface receptors, including receptor for advanced glycation end-products (RAGE) (13) and toll-like receptors (TLRs) (14,15), to initiate functional responses by activating downstream signaling pathways. This results in the activation of immune cell activities, the induction of proinflammatory cytokines, stimulation of cell adhesion and migration, promotion of cell proliferation and angiogenesis, and induction of autophagy (16-18).

Although it has been previously suggested that upregulated expression of HMGB1 is associated with lung cancer, the underlying mechanisms of lung cancer oncogenesis and progression remain to be fully elucidated. The present study aimed to summarize the effects of HMGB1 on the oncogenesis and progression of lung cancer, and to reveal the hallmarks and potential therapeutic targets of this mechanism.

2. Receptors and regulation

HMGB1 serves an important role in the generation and development of lung cancer (19). The role of HMGB1 in mediating carcinogenesis and metastasis of lung cancer has been previously investigated. HMGB1 is associated with RAGE and TLRs via three primary pathways, including phosphoinositide-3-kinase (PI3K)/RAC-α serine/threonine-protein kinase (Akt), nuclear factor-κB [NF-κB (P56)], and mitogen activated protein kinase (MAPK) [extracellular signal-regulated kinase 1/2 (ERK1/2), p38)].

RAGE. This protein belongs to the immunoglobulin superfamily of transmembrane proteins, and is shared by numerous ligands, including HMGB1 and amphoterin (20,21). The co-expression of HMGB1 and RAGE is associated with the invasive and metastatic potential of hepatocellular carcinoma (22-24). In normal human bronchial epithelial cells, the HMGB1-induced inflammatory response promotes the activities of the RAGE/c-Jun N-terminal kinase 1 (JNK)/NF-κB pathway by binding to RAGE (25,26). The pro-inflammatory activity of HMGB1 is associated with the pathogenesis of precancerous lesions (27,28). RAGE also interacts with amphoterin, which contributes to tumor growth and metastasis (29). Compound NBRI17671 (2) is a RAGE inhibitor that downregulates MAPK activity and effectively inhibits the growth of lung tumor xenografts in mice (30). This phenomenon maybe attributed to the blockade of RAGE-amphoterin. Notably, RAGE is highly expressed in normal tissues, particularly in the lungs (31). However, the expression level of RAGE in the serum and tissue of patients with lung cancer is lower compared with that of normal lung tissue (32-34).

HMGB1 promotes cancer cell migration and invasion, as well as angiogenesis, growth and metastasis of cancer by regulating matrix metallopeptidase 9 (MMP-9) in lung cancer (28,29). HMGB1 expression is positively associated with MMP-9 expression (35). The potential mechanism involves the formation of a HMGB1-RAGE complex, which activates MAPK signaling pathways and MMP-9. Following MMP-9 activation, the extracellular matrix is degraded, allowing tumor invasion and metastasis to occur (36,37). HMGB1-induced MMP-9 expression has been reported to be associated with tumor metastasis in NSCLC. The overexpression of HMGB1 activates MMP-9 by triggering the PI3K/Akt and NF-κB signaling pathways (38).

TLRs. These pattern recognition receptors activate a cascade of downstream signals, resulting in the secretion of inflammatory cytokines, chemokines and type I interferons (39,40). TLRs are evolutionary conserved from invertebrates to humans, and the TLR family has ≥13 members (41). TLR2, 4 and 9 have been identified as receptors of HMGB1 (42). TLRs have also recently emerged as key immunomodulators of the immune response in carcinogenesis and tumor progression (43).

TLR2 is an inflammation-associated receptor, expressed on megakaryocytes and platelets (44). It has been implicated in inflammation-induced platelet activation and vascular diseases (45). Elevated expression of TLR2 and its functional activation are exhibited by monocytes of patients with type 2 diabetes mellitus, suggesting a molecular association between inflammation and diabetes (46). A previous study demonstrated HMGB1 to be a ligand, which endogenously activates TLR2 in several pathological conditions (47). HMGB1 is released during exposure to acute hypoxia and activates TLR2 (48). Activated TLR2, in turn, induces the upregulation and secretion of von Wille brand factor, thus promoting insulin resistance (48). Another study demonstrated that HMGB1 upregulates the expression of TLRs in natural killer (NK) cells and promotes the maturation of NK cells in ageing mice. The activation of NK cells lead to an increased and persistent immune response in cholangiocytes, inducing biliary atresia (49). In human and mouse breast cancer stem cells (CSCs), the HMGB1/TLR2 axis promotes NF-κB activation, interleukin-6 and transforming growth factor-β production, as well as signal transducer and activator of transcription 3, and SMAD family member 3 activation. These cytokines are known to affect CSC self-renewal and tumor-generating ability (50).

TLR4 is a receptor of HMGB1, and NF-κB and MAPK expression levels are increased when TLR4 is activated by HMGB1 (51,52). NF-κB and MAPKs regulate the expression of inflammatory genes, and participate in the proliferation, invasion and metastasis of tumor cells (52). One study demonstrated that the interaction between TLR4 on platelets and tumor-cell HMGB1 promotes the metastasis of Lewis lung carcinoma (LLC) tumor cells *in vitro* and *in vivo* (53). Therefore, TLR4 mayact as a therapeutic target to prevent platelet-mediated tumor metastasis.

HMGB1 was reported to be involved in the regulation of cell autophagy at the transcriptional level (54). Reciprocally, it has been suggested that autophagy regulates the induction of HMGB1 secretion (55). Following its upregulation, HMGB1 translocates from the nucleus to the cytoplasm in Lewis cells upon nutrient depletion. The starvation of Lewis cells promotes HMGB1 secretion, which induces autophagy and inhibits apoptosis by activating a RAGE-HMGB1/ERK1/2-dependent pathway (56). This indicates that HMGB1 overexpression may serve as a Lewis lung carcinoma risk factor, stimulating cancer growth and metastasis. Another study reported that HMGB1 significantly stimulates the proliferation of Lewis cells and inhibits apoptosis *in vitro* via the HMGB1-RAGE/TLR4-PI3K/Akt or HMGB1-RAGE/TLR4-ERK1/2 pathways (55). Thus, there is conflicting evidence regarding the contribution of HMGB1 to apoptosis and proliferation. However, these findings provide a basis for future investigations.

TLR9 is localized in the endoplasmic reticulum, but redistributes to early endosomes upon activation by CpG-DNA or synthetic CpGoligodeoxynucleotide (ODN) analogs (57,58). HMGB1 acts as a CpG-ODN-binding protein. CpG-ODN stimulates macrophages and dendritic cells to secrete HMGB1. HMGB1 enhances the immunostimulatory potential CpG-ODNs in a TLR9-dependent manner (54). Activated TLR9 recruits Myeloid differentiation primary response protein MyD88 (MyD88), allowing the execution of subsequent immune responses (59). The interaction between TLR9 and CpG ODN promotes 95D cell proliferation *in vitro*, and *in vivo* (36,60). On the basis of these studies, Wang *et al* (37) indicated that extracellular HMGB1 contributes to the proliferation of lung cancer 95D cells via MyD88-dependent RAGE

and TLR4 signaling. Sun *et al* (61) also reported that HMGB1 functions in the regulation of ERK1/2 and p38 MAPK signaling pathways, which are implicated in the proliferation, and invasion of lung cancer cells. P38 and ERK1/2, activated by HMGB1, transcriptionally regulate NF-κB, resulting in cell proliferation and lung cancer development (61).

3. Role of HMGB1 in lung cancer

HMGB1 expression in patients with lung cancer. HMGB1 has been associated with the prognosis of patients with lung. The expression levels of HMGB1 in the tissue and serum of patients with lung cancer are significantly higher compared those of normal lung tissue samples (62,63). HMGB1 levels are positively associated with tumor size, tumor node metastasis stage and distant metastasis (42). In patients with NSCLC, the serum level of HMGB1 detected one month subsequent to surgery was significantly increased compared with the pre-operative level (43). An increased level of HMGB1 in the serum of patients with progressive NSCLC was associated with shorter overall survival and disease-free survival times (64). Therefore, HMGB1 may be considered as a potential biomarker for the diagnosis and prognosis of patients with NSCLC (45,46). There is varying evidence regarding the average expression level of HMGB1, due to heterogeneity of detection methods, small sample sizes and low statistical power (42). Thus, whether HMGB1 is over- or underexpressed in patients with lung cancer remains unclear, and requires confirmation and clinical validation (19).

HMGB1 and tumorigenesis. As HMGB1 expression has been demonstrated to be increased in lung cancer tissue, serum and cell lines, researchers have suggested that the overexpression of HMGB1 contributes to the development, and progression of lung cancer (61). The underlying molecular mechanisms regarding the contribution of HMGB1 to the progression of lung cancer have been investigated. It was indicated that HMGB1 enhances the growth of 95D cells through acting synergistically with CpG-ODN (37). Another study reported that HMGB1 exerts its effects by regulating ERK1/2 and p38 MAPK signaling pathways, which are both implicated in cell proliferation, and lung cancer development (61).

Cytoplasmic HMGB1 binds beclin 1 (65,66), and p53 is a negative regulator of the HMGB1/beclin 1 complex. The exogenous HMGB1 promotes autophagy in tumor cells through interactions with RAGE (67,68). HMGB1 binds to p53 to regulate the cytoplasmic localization of the HMG1/beclin 1 complex (69). The HMGB1/p53 complex also regulates the balance between tumor cell death and survival (70). A previous study reported that p53-knockout in human colorectal cancer cells increased the expression of cytosolic HMGB1 and upregulated autophagy (70). However, to the best of our knowledge, the role of the HMGB1/p53 complex in lung cancer has not been previously reported.

HMGB1 and metastasis. Metastasis is a hallmark of malignant tumors, and the principal cause of mortality in patients with lung cancer (41). NF-κB p65 was initially identified in mature immune cells and was reported to regulate cellular functions through various signaling pathways (71). p65 is positively associated with metastasis (62). Zhang *et al* (71) observed that p65 expression in patients with NSCLC was remarkably higher compared with that in healthy patients. Furthermore, the protein expression levels of HMGB1 and p65 were significantly higher in patients exhibiting lymph node metastasis compared with patients without metastasis. Correlation analysis revealed that HMGB1 and p65 protein expression levels are positively correlated with NSCLC metastasis (71).

MicroRNAs (miRNAs) inhibit cancer cell migration and invasion through the suppression of HMGB1 (66-68). miRNAs affect mRNA cleavage or translational repression by directly targeting the 3'-untranslated region of HMGB1 mRNA (66). Zhang *et al* (72) observed that miR-218 overexpression negatively regulated HMGB1 expression at the mRNA and protein levels, and further inhibited cell migration and invasion in human lung cancer cell lines, A549 and H1299. The expression of miR-325-3p was demonstrated to be negatively correlated with that of HMGB1 in human lung cancer tissues (73). Patients with NSCLC exhibiting low miR-325-3p expression had significantly shorter overall and progression-free survival times compared with patients exhibiting high miR-325-3p expression. These results indicate that the overexpression of miR-325-3p may indicate good prognosis, and act as a potential prognostic and predictive marker for patients with NSCLC (73). Further investigation demonstrated that miR-142-3p may modulate cell tumorigenesis by targeting HMGB1 in NSCLC (74). Another study indicated that miR-181b directly targeted HMGB1 in NSCLC cells and that miR-181b has been demonstrated to inhibit NSCLC cell motility (75). These results suggest that miR-142-3p and miR-181b may be novel therapeutic agents to prevent NSCLC from becoming invasive (74,75). Zhu *et al* (76) reported that HMGB1 enhances the metastatic ability of NSCLC cells by activating αvβ3/focal adhesion kinase through the TLR4/NF-κB signaling pathway.

HMGB1 and chemotherapy resistance. In various treatment regimens for lung cancer, chemotherapy is often the first line of treatment for patients with lung cancer, particularly NSCLC (77,78), and cisplatin (DDP) and carboplatin are commonly used drugs. However, several survival mechanisms, including anti-apoptosis, drug resistance and immune defense, compromise the therapeutic efficacy of these drugs (79-81). HMGB1 is highly expressed in NSCLC cell lines. The levels of HMGB1 in NSCLC cells treated with chemotherapeutics were increased compared with untreated cells. The expression of autophagy-associated proteins beclin 1 and LC3-II were significantly higher in DDP-resistant cells compared with A549 cells treated with chemotherapeutic drugs (7). These data suggest that HMGB1 expression is associated with drug resistance. HMGB1-induced cell autophagy inhibited cell apoptosis in DDP-resistant lung cancer cells (7). Another mechanistic investigation revealed that HMGB1 inhibited apoptosis and increased drug resistance through activating the MAPK-ERK signaling pathway, thereby promoting the formation of the beclin-1-PI3K-III complex (82).

The function of HMGB1-associated proteins in chemotherapy-induced DNA damage has been assessed in human carcinoma A549 cells by gene knockdown using short interfering RNAs (83). This revealed that the chemosensitivity of A549 cells to cytarabine was decreased by 8-50 fold, and that

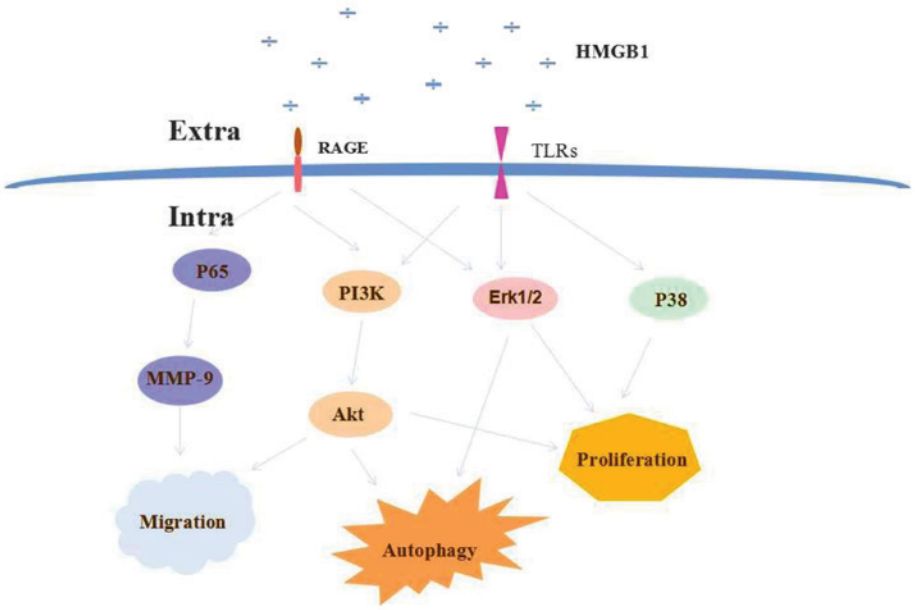

Figure 1. HMGB1 modulates cell proliferation, cell death and metastasis. The overexpression of HMGB1 induces the activation of PI3K/Akt, NF-κB (p56) and MAPK (ERK1/2, p38) signaling pathways by binding to RAGE or TLRs on lung cancer cells. HMGB1, high-mobility group protein B1; PI3K, phosphoinositide-3-kinase; NF-κB, nuclear factor-κB; MAPK, mitogen activated protein kinase; ERK, extracellular signal-regulated kinase 1/2; RAGE, receptor for advanced glycation end-products; TLR, toll-like receptor; MMP9, matrix metallopeptidase 9; extra, extracellular; intra, intracellular.

HMGB1 and HMGB2 participate in this process by modulating p53 phosphorylation (83). These results improve the existing understanding of the mechanism of chemotherapy resistance. Aranda *et al* (84) demonstrated that pyridoxine, a precursor of vitamin B6, increases the immunogenicity of cisplatin-induced cell death in patients with NSCLC. This may have important implications for the development of novel strategies to circumvent cis-diamminedichloroplatinum (II) resistance.

4. HMGB1-targeting therapeutic strategies

Lung cancer may be treated by inhibiting HMGB1 production. Although research on this rationale has been conducted *in vitro* and *in vivo*, clinical studies are yet to be performed. Therefore, direct evidence of the potential efficacy of therapeutic strategies targeting HMGB1 in lung cancer is not yet available (85).

Sodium salicylate. Sodium salicylate, which is the active metabolite of aspirin, elicits anti-inflammatory activity by inhibiting the expression or activation of various pro-inflammatory factors, including cyclooxygenase 2, inducible nitric oxide synthase and interleukin-1β (85). Sodium salicylate is also involved in defense against tumor development and progression (86). Sodium salicylate may potentially suppress the release of HMGB1 from necrotic cells by redirecting glucose deprivation-induced necrosis to autophagy; as a result, inflammatory responses and tumor development are prevented (87). Therefore, sodium salicylate may be used as a novel agent for the control and treatment of lung cancer.

Ethyl pyruvate (EP). EP inhibits the levels of HMGB1 secreted from endotoxin-stimulated macrophages (88). EP has been applied to HMGB1-associated therapeutic strategies for hepatocellular carcinoma in animal models (89). EP reportedly induces the death of lung adenocarcinoma A549 cells (88). The underlying mechanism of EP is similar to that of sodium salicylate. Guo *et al* (90) suggested that EP significantly inhibits the development of murine colitis by inhibiting HMGB1-T-helper 17 (Th17) and Th1/transcriptional and immune response regulator responses. These results may provide a novel perspective on the interaction between EP and HMGB1.

5. Conclusions and perspectives

In summary, HMGB1 overexpression is involved in various diseases, including lung cancer. HMGB1 has been demonstrated to induce tumorigenesis, metastasis and chemotherapeutic responses in lung cancer. HMGB1 receptors involved in lung cancer progression include RAGE and TLRs. The effects of HMGB1 are executed via various signaling pathways, including PI3K/Akt, NF-κB (p65) and MAPK (ERK1/2, p38). A schematic illustration of HMGB1 signaling in lung cancer is presented in Fig. 1.

The present study summarizes the association between HMGB1 with the oncogenesis and progression of lung cancer. It not only elucidates the molecular mechanism of carcinogenesis and progression of lung cancer, but also provides a reliable basis for further investigation. HMGB1 may be a potential treatment target for early disease diagnosis. It may have potential in therapeutic research for lung cancer, and thus required further investigation.

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Authors' contributions

LY participated in the conception and design of this work. LW searched the literature, and drafted and revised the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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