Review Article

High Motility Group Box 1 Induces Cancer Aggressiveness and Drug Resistance

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Abstract

High motility group box 1 (HMGB1) is a non-histone chromosomal protein; it is a secretory protein that binds to receptor for advanced glycation end products (RAGE) in cancer cells and monocyte-lineage immune cells. HMGB1 enhances proliferation, motility, invasiveness, and survival of cancer cells. HMGB1 is associated with the repair of DNA damage induced by anticancer drugs. Importantly, it is released from necrotic cancer cells and induces regrowth of remnant cancer cells. In contrast, HMGB1 induces apoptosis in monocyte-lineage immune cells and inhibits tumor-infiltrating macrophages and dendritic cells, lymph node sinus macrophages, and liver Kupffer cells to attenuate anticancer immune responses and anti-metastatic organ defense.

ABBREVIATIONS

HMGB1: High motility group box 1; **RAGE**: receptor for advanced glycation end products; **TLR**: toll-like receptor, **MAP**: mitogen-activated protein; **MMP**: matrix metalloproteinase; **iNOS**: inducible nitric oxide synthase; **NF**: nuclear factor; **VEGF**: vascular endothelial cell growth factor; **HIF**: hypoxia-inducible factor; **JNK**: c-Jun N-terminal kinase; **OSCC**: oral squamous cell carcinoma; **CRC**: colorectal cancer; **KC**: Kupffer cell, **DC**: dendritic cell; **PMDDC**: peritoneal macrophage-derived dendritic cell; **DXR**: doxorubicin; **TSA**: trichostatin A; **MDR**: multiple drug resistance

INTRODUCTION

High motility group box (HMGB)-1 is a multifunctional protein involved in diverse biological activities in normal cells. The roles of HMGB1 in cancer are also diverse and can be divided into 2 categories: direct effects on cancer cells and effects on host immunity. HMGB1 shows pro-tumoral and anti-immune effects in cells expressing receptor for advanced glycation end products (RAGE). Both cancer cells and monocyte-lineage cells express RAGE; however, its role differs between the two cell types. Essentially, HMGB1 accelerates the metastasis of cancer cells. In this review, we describe the roles of HMGB1 in cancer cells and immunity, and its effect on anticancer drugs and tumor re-growth after anticancer treatment. The significant roles of HMGB1 in cancer suggest that it is an excellent molecular target for cancer treatment, especially anti-metastatic therapeutics. Combined, these roles of HMGB1 confer resistance to anticancer drugs.

HMGB1 IN CANCER

HMGB1

HMGB1 is one of several non-histone chromosomal proteins found in eukaryotic cells [1-3]. It was isolated as a cytosolic 30-kDa protein from fetal brain tissue [4,5] and it is associated with neurite outgrowth [2,3]. As a nuclear protein, HMGB1 binds to DNA participating in multiple processes such as transcription, replication, recombination, DNA repair, and genomic stability [6].

In the cytoplasm, HMGB1 is associated with cell motility as observed in the outgrowing neuritis. At the leading edge of the motile cell, HMGB1 accelerates the formation of filopodia and actin polymers [2]. The mechanism of HMGB1-dependent cell migration in cancer cells is considered to be similar to that of neurite outgrowth. HMGB1 is expressed in immature cells and malignant cells at high levels and it plays a major role in controlling cell migration [7]. Due to its DNA-binding capacity, HMGB1 acts as a DNA chaperone. In the innate immune system, it is an effective DNA sensor for toll-like receptor (TLR) [8]. Recently, endogenous HMGB1 has been revealed to activate an autophagy signal, which promotes cell survival [9].

HMGB1 is secreted from activated monocytes, macrophages, and NK cells, and acts as an extracellular proinflammatory cytokine. HMGB1 expression and secretion are upregulated in response to stimulation of cells by proinflammatory cytokines, endotoxins, and oxidative stresses in macrophages [10-13]. Cancer cells also overexpress and secrete HMGB1

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when stimulated by growth factors, cytokines, and cellular stresses involving advanced glycation end products (AGE) and deoxycholic acid [14-17]. Secreted HMGB1 activates RAGE as a ligand to induce cell growth, motility, invasion, and angiogenesis, as will be described below.

HMGB1 receptor

The HMGB1 receptor, RAGE, is purified from bovine lung endothelial extracts as a receptor of AGE [18]. RAGE is a cell surface receptor belonging to the immunoglobulin superfamily [19-22]. It is closely associated with cell growth, cell invasion through activation of mitogen-activated protein (MAP) kinase, and matrix metalloproteinase (MMP)-2/-9 expression in glioma cells [22]. RAGE upregulation is found in colon and oral carcinogenesis in rodents [16,23].

The co-expression of HMGB1 and RAGE is pivotal for accelerating tumor metastasis and poor prognosis in glioma, gastric, colorectal, and prostate cancers [15,22, 24-26]. Gastric and colon cancer cells show concurrent expression of HMGB1 and RAGE, which is closely associated with the autocrine/paracrine regulation of cell motility and invasion of cancer cells [15,24-26]. Metastatic prostate cancer cases show HMGB1 induction in prostatic stromal cells. Concurrence of RAGE expression in tumor cells and HMGB1 expression in stromal cells accelerates cancer metastability [15].

In contrast, RAGE and HMGB1 are expressed at high levels in normal lung tissue and non-small cell lung cancer, which, unlike other cancer types, is associated with tissue differentiation and good prognosis [27, 28]. RAGE is also associated with myogenic differentiation of myoblasts and rhabdomyosarcomas, which are associated with the reduction of malignant phenotypes of the disease [29,30].

HMGB1 secretion

HMGB1 is released by both active and passive processes. HMGB1 is actively transported from the nucleus to the cytoplasm following detachment from loosened chromosomes by histone acetylation [17]. Recent studies have shown that in macrophages, it shuttles between the nucleus and the cytoplasm through hyperacetylation and phosphorylation and that in neutrophils, it is monomethylated at Lys42. HMGB1 is released from necrotic cells by passive diffusion [31]. However, it is not released from the tightly packed nuclei of apoptotic cells and triggers inflammation.

HMGB1 intracellular signals

The interaction of HMGB1 with RAGE also activates the intracellular signaling pathway of MAP kinase. Consequently, RAGE activates GTPases, Ras, Cdc42, Rac, Rho, and MMP-2/-9 [3,22]. RAGE expression is associated with cell invasion [24,26] and it is suggested that type IV collagenase activation may be one mechanism for enhancing the invasive capacity of cancer cells. RAGE activation induces cell growth through MAP kinase signaling [22], and is associated with the stimulation of inducible nitric oxide synthase (iNOS), nuclear factor (NF) κB activation, and Bcl-2 production [32]. NFκB activation is associated with HMGB1-dependent chemotaxis [33].

HMGB1 and angiogenesis

The intracellular signaling pathways involving RAGE induce vascular endothelial cell growth factor (VEGF) expression and activate NF-κB in vascular endothelial cells [34]. Activated RAGE induces VEGF expression transcriptionally via activation of NFκB, AP-1, and hypoxia-inducible factor (HIF)-1α [34, 35], which is also associated with complications related to diabetes, such as diabetic retinopathy [36]. VEGF induction differs between AGE and HMGB1 [26]. AGE-BSA has a more pronounced effect on VEGF expression than does HMGB1 in colorectal cancer (CRC) cell lines. In our studies, HMGB1 induced the secretion of VEGF but not that of VEGF-C in human oral squamous cell carcinoma (OSCC) cell lines [37]. VEGF-C and VEGF-D are associated with lymph node metastasis [38]. Differential induction of VEGF from VEGF-C through activation of RAGE by HMGB1 may explain why RAGE expression is not associated with lymphangiogenesis. Lymph node metastasis of cancer is strongly associated with lymphangiogenesis [39].

HMGB1 in anticancer immunity

HMGB1 is associated with a significant reduction of intratumoral macrophage infiltration in metastatic colon cancer [40]. HMGB1 induces growth inhibition in rat peritoneal macrophages, U937 human monocytes, and human alveolar macrophages, and it induces apoptotic death with phosphorylation of JNK and Rac1, and upregulation of caspase-3 and caspase-9 [41,42]. JNK is associated with apoptotic signals transmitted by Rac1/Cdc42 [29,30,43].

Tumor-associated macrophages also have anticancer effects [44]. In clinical studies, colon cancer patients with high-level macrophage infiltration show less invasion and metastasis than those with low-level macrophage infiltration [45]. Depletion of tumor-infiltrating macrophages is closely associated with advanced stages of human colon cancer and with metastatic ability in a mouse colon cancer model [40]. Dukes B CRC cases demonstrate macrophage-cancer cell contact, whereas Dukes C cases showed no such contact. HMGB1 expression is associated with macrophage depletion in colon cancer tissues [40].

Lymph sinus macrophages and liver Kupffer cells (KCs) participate in the immune response against metastatic cancer cells in these organs. Sinus macrophages and KCs mediate the phagocytosis of cancer cells attached to the sinus wall in order to inhibit their metastasis [46,47].

In CRC cases, macrophage numbers in the regional lymph nodes are decreased in both non-metastasized and metastasized nodes in Dukes C cases, whereas macrophage numbers are higher in Dukes B cases than those in Dukes C cases [48]. The nodal HMGB1 concentration is higher in Dukes C nodes than that in Dukes B nodes; this is inversely correlated with macrophage numbers. Nodal HMGB1 concentration is correlated with HMGB1 concentration and the lymph vessel density found in the primary tumors [48]. A high concentration of HMGB1 is reported in effusions from cancer patients. These data indicate that HMGB1 secreted from primary tumors is delivered to the regional lymph nodes and decreases the number of macrophages to weaken the anti-metastatic defense of the lymph nodes in patients with CRCs.

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In a nude mouse liver metastasis model, the cecal administration of HMGB1 decreased the number of KCs and increased the embedment of colon cancer cells in a dose-dependent manner [49]. HMGB1 is secreted from the primary tumors of colon cancer and delivered to the liver through portal blood flow. Following this, HMGB1 inhibits KCs and accelerates liver metastasis of colon cancer. In clinical studies, higher HMGB1 concentrations are found in primary tumors and metastatic foci, and fewer KCs are found in Dukes D cases than in Dukes C cases. The portal blood HMGB1 concentrations are higher in Dukes D cases than in Dukes C cases. We have also shown that the concentration of HMGB1 in the portal blood is strongly correlated with the concentration of HMGB1 in primary tumors [49]. As a result, HMGB1 affects host immunity in the metastasis target organs in a humoral manner. Large amounts of secreted HMGB1 can affect remote organs such as the target organs of metastases from CRCs.

Dendritic cells (DCs) play a crucial role in host immune responses to various extrinsic microorganisms and to cancer cells [50]. Dendritic cell densities in primary tumors and metastatic tumors are suppressed [51]. Indeed, nodal metastasis-positive colon cancer cases show higher HMGB1 concentrations in lymph nodes and primary tumor tissues, and fewer dendritic cell numbers than metastasis-negative cases [42]. HMGB1 produced by colon cancer cells results in a suppression of nodal dendritic cells to attenuate host anticancer immunity. HMGB1 results in the activation of monocytes and dendritic cells; however, high concentrations of HMGB1 result in the death of dendritic cells, as observed on macrophages [42]. Mouse peritoneal macrophage-derived dendritic cells (PMDDCs) treated with HMGB1 show a decrease in the cell number in a dose-dependent manner. HMGB1-treated PMDDCs show apoptosis and increased levels of phosphorylated JNK, and intraperitoneal administration of HMGB1 decreased splenic dendritic cells in C57BL mice [42].

HMGB1 may be related to increased cancer progression and suppression of host immunity; therefore, further examination of the role of HMGB1-induced macrophage apoptosis in cancer cells may provide novel therapeutic targets against these diseases.

HMGB1 and anticancer drugs

HMGB1 proteins bind with high affinity to specific structural distortions in the double helix such as synthetic four way junctions and adducts that are formed in DNA modified by the anti-tumor drug cisplatinum and UV light [52,53]. DNA-bound HMGB1 plays a role in DNA repair, providing drug resistance to platinum derivatives in cancer cells [54].

HMGB1 is passively secreted from necrotic cells. We have confirmed that necrosis inducers such as doxorubicin (DXR) increase HMGB1 concentration in the cultured medium. In contrast, apoptosis inducers such as trichostatin A (TSA) do not increase HMGB1 in the cultured medium. In a mouse tumor model of bilateral scapular subcutaneous tumors, induction of necrosis in one tumor by DXR enhances the growth of a contralateral tumor. In contrast, induction of apoptosis in one tumor by TSA does not affect the growth of a contralateral tumor. Moreover, in mouse liver and lung metastasis models with a single subcutaneous tumor, induction of necrosis at the subcutaneous
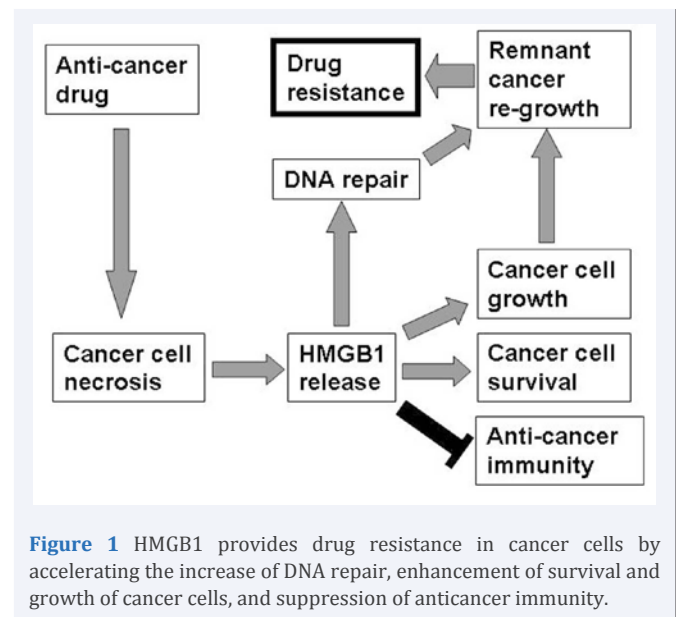

Figure 1 HMGB1 provides drug resistance in cancer cells by accelerating the increase of DNA repair, enhancement of survival and growth of cancer cells, and suppression of anticancer immunity.

tumor by DXR increases metastasis to the liver and lung. The enhancement of metastasis is abrogated by the administration of anti-HMGB1 antibody. These findings suggest that HMGB1 enhances growth of the remnant cancer cells, increasing tumor relapse and metastasis. Pro-apoptotic but not pro-necrotic anticancer drugs are needed to avoid HMGB1-induced cancer relapse and metastasis.

CONCLUSION

HMGB1 accelerates aggressiveness of cancer including reflection to anti-cancer drugs. Drug resistance is provided secondarily by enhancement of tumor survival and reduction of anticancer immunity. HMGB1 accelerates the drug resistance of cancer cells by increasing DNA repair, suppression of anticancer immunity, and enhancement of survival and growth of cancer cells (Figure 1). In this context, HMGB1 is a pivotal anticancer drug-resistant factor. To increase the efficacy of anticancer treatment, HMGB1 is a relevant target.

ACKNOWLEDGEMENTS

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