Potential role of High mobility group box 1 in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and is characterized as a typical inflammation-related carcinoma. High mobility group box protein 1 (HMGB1), a non-histone DNA-binding protein, is identified as a potent proinflammatory mediator when presents extracellularly. Recently, a growing body of evidence indicates that HMGB1 plays a potential role in HCC, but many questions remain unanswered about the relationship between HMGB1 and HCC formation and development. This review focuses on the biological effect of HMGB1, and discusses the association of HMGB1 with HCC and potential use of strategies targeting HMGB1 in HCC treatment.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related deaths globally.1,2 Despite the significant progress obtained in molecular biology and cancer therapy, the overall survival of HCC remains poor, which was mainly attributed to lack of early diagnosis, distant metastasis, therapy resistance and local recurrence. Since the molecular mechanisms contributing to generation and development of HCC are complex, referring to multiple factors and stages, clarification of these processes remains a big challenge. HCC is characterized as an inflammation-related carcinoma, and approximately 90% of HCC are closely related to chronic liver disease,3 such as autoimmunity, trauma4 and cancer.5 Overexpression of HMGB1 has been detected in carcinomas of the breast,6 tumors of the gastrointestinal tract,7 malignant lymphomas8 and also hepatocellular carcinoma.9 It is presumed that within the tumor microenvironment, extracellular HMGB1 can induce chronic inflammation and contributes to the process of initiation, promotion and metastasis of tumor cells (Fig. 1).

Although many researches revealed that the expression of HMGB1 relates to HCC, questions remain unsolved about the mechanisms that how HMGB1 promotes the process of HCC. In this review, we will discuss the role of HMGB1 in HCC formation and development focused on the current understanding.

Biological Effect of HMGB1 in Tumor Development

HMGB1 and its receptors

Combination of HMGB1 and RAGE

Receptor for advanced glycation end product (RAGE), a member of the immunoglobulin superfamily of cell surface molecules, is a main receptor of HMGB1. Many studies point out the co-expression of HMGB1 and RAGE correlated with development and metastasis of tumors.14-16 Extracellular HMGB1 combines with RAGE and subsequently activates intracellular signals, by this way regulates tumor growth and metastasis.17 Two pathways related to HMGB1 and RAGE combination has been identified, they were Rac and Cdc42 pathway and MAPK and NF-kappa B pathway.18 HMGB1/RAGE complex can influence invasion of tumor cells by activating p38, JNK, MAPK and p42/p44 MAPK pathway. Besides, RAGE and HMGB1 coordinately enhances tumor cell mitochondrial complex I activity, ATP production, tumor cell proliferation and migration. Lack of RAGE or inhibition of HMGB1 release diminishes ATP production and down-regulates tumor growth in vitro and in vivo.19 Interestingly, one research indicates that the coexistence of high level of HMGB1 and RAGE does not exist in all types of tumors, for high expression of RAGE was absent despite the high expression of HMGB1 in malignant testicular specimens.13,20

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**HMGB1 and Toll-like receptor**

Toll-like receptors are also important in HMGB1 signaling pathways, and TLR2, TLR4 and TLR9 are all receptors of HMGB1. TLRs is Type I trans-membrane protein participated in the signal transfer of TLR pathways and HMGB1. Activation of TLR signaling by HMGB1 can finally activate NF-kappa B and MAPKs and regulate gene expression of inflammatory and other concerned mediators, thus participates in proliferation, invasion, and metastasis of tumor cells. On the other side, HMGB1 released from apoptotic cells interacts with TLR4 of dendritic cells, induced release of MCP-1, IP-10 and MIP-1α in a TLR4- and CD14-dependent manner, which subsequently activates tumor T lymphatic cells and generates anti-tumor effects.

**HMGB1 and JAK/STAT pathway**

HMGB1 could modulate the inflammatory reaction in JAK/STAT pathway, which has great impact on development and generation of tumor. STAT is highly expressed in malignant tumors, while little or none is expressed in normal tissues or cells. Activation of JAK/STAT pathway induces over-activation of STAT, especially STAT3, which inhibits tumor cell apoptosis and promotes progression of cell cycles.

**HMGB1 and immune reactivity**

HMGB1 has a strong relationship with immune reactivity. It modulates the biological activities of Treg for it can induce migration and prolonging survival of this cell. HMGB1 enhances suppressive capacity of Treg in cancers in a RAGE-dependent manner. In addition, HMGB1 directly suppresses interferon-gamma (IFN-gamma) release of conventional T cell (Tcon) and inhibits their proliferation via TLR4. The effects of HMGB1 on Treg may alter immune reactivity in the setting of chronic inflammatory states such as cancer.

**Role of HMGB1 in HCC**

**HMGB1 in patients with HCC**

In clinical studies, HMGB1 links with clinical outcome and prognosis of HCC patients. Serum level of HMGB1 in HCC patients is significantly higher than that in chronic hepatitis, liver cirrhosis patients and healthy controls. Higher level of serum HMGB1 is correlated with larger tumor size, worse tumor stages and pathological differentiation grades of these patients. Level of HMGB1 in both mRNA and protein level in tumor tissue elevates significantly when compared with para-tumor and normal tissue, and this could predict the prognosis of HCC. Expressions of HMGB1 protein within HCC tissue among different Edmondson grades, TNM stages and Cancer of the Liver Italian Program scores are significantly distinct, which indicated that high expression of HMGB1 may predicts poor prognosis for patients with HCC.
HMGB1 in tumor microenvironment of HCC

The tumor microenvironment is a concept that the behavior of cancer is not only related to genetics of tumor, but also its surrounding environment that tumor cells need for survival, growth, proliferation, and metastasis. Components of the HCC microenvironment comprise cellular elements, cytokines, growth factors and several proteins. The chronic inflammatory status of the liver such as infected with hepatitis viruses caused changes in microenvironment including the extracellular matrix (ECM), hepatic stellate cells (HSCs) and HMGB1.30,31 This had been proved by previous studies that HMGB1 serum levels were significantly higher in patients with chronic HBV infection than in controls.32-34 HMGB1 can signal through RAGE and through TLRs. Activation of these receptors ultimately results in the activation of NF-kappaB, which in turn induces the up-regulation of leukocyte adhesion molecules, production of pro-inflammatory cytokines and angiogenic factors in both hematopoietic and endothelial cells, thereby promoting inflammation and providing a permissive milieu for the development of cellular dysplasia and ultimately HCC (Fig. 1).35,36

P53 is attributed to be a tumor suppressor, closely associated with apoptosis, autophagy and metabolism of human cancer cells, and findings indicates that HMGB1 interacts with p53. Up to now, several researches suggest that p53/HMGB1 plays important role in carcinogenesis, for it may inhibits the abnormal growth of tissue cells to avoid canceration, but on the other hand it may simultaneously activate tumor associated inflammation which is prof in tumor generation.37 Knockout of p53 in human colorectal cancer cell HCT116 cells increases expression of cytosolic HMGB1 and induces autophagy, and this process may help these tumor cells survive. Furthermore knock-down of HMGB1 with HMGB1 shRNA or HMGB1 inhibitor attenuate p53 deficiency-induced autophagy. Studies with a rat model of carcinogen-induced hepatocarcinogenesis, observes that translocation of HMGB1 into the cytoplasm in hepatocytes and serum levels of HMGB1 significantly decreased in p53+/- rats than wild type following carcinogen administration. Restoration of p53 expression in p53-null hepatocytes or induction of p53 in wild type hepatocytes greatly elevates release of HMGB1.38 These findings suggest that p53 promotes pro-tumorigenic inflammation by inducing release of HMGB1 in HCC development.39

HMGB1 in growth of HCC cells in vitro

HMGB1 released from damaged tumor cells induced by chemotherapy, enhances regrowth and metastasis of cancer cells that have survived after chemotherapy in many types of malignancy.44-46 HMGB1 plays an indispensable role in generation and development of HCC in in vitro experiments. HMGB1 can affect the level of some cytokines, pathways and expression of genes closely related to cancers, for example low concentration of HMGB1 could up-regulates the expression of IL-6 and IL-8 in HepG2 cells. Exogenous HMGB1 increases cell proliferation by up-regulates expression of Cyclin D1 and PCNA, while using anti-HMGB1 antibodies not only neutralizes this effect but also down-regulates growth of HepG2 cells.43 When specific small interfering RNAs, that could significantly inhibits expression of HMGB1, are transfected into HCC cell lines HCCLM-3/HepG2 cells, the proliferation, migration and invasive ability of these cells diminishes notably and apoptosis increases markedly.44,45 Further studies identifies that the inhibition of HMGB1 is accompanied with the decrease of NF-kappa B/p65, which suggests that HMGB1 regulates biological activity of HCCLM-3 cells through NF-kappa B transcription factor.43

HMGB1 in metastasis of HCC

HMGB1 is also associated with metastasis of HCC, for it activates caspase-1 and consequently promotes invasiveness and metastases of hepatocellular carcinoma. In hypoxic HCC cells, HMGB1 activates TLR4- and RAGE-signaling pathways to induce caspase-1 activation. Following caspase-1 activation, cleavage and release of proinflammatory cytokines interleukin (IL)-1 β and -18 occurred, which in turn, promotes cancer invasion and metastasis.46 It is also reported that knock-down of HMGB1 inhibits liver cancer cell growth and metastasis through AKT-mediated down regulation of Ki-67 and MMP-2 expression.47 Lymphangiogenesis is an indicator of metastasis, and HMGB1 promotes lymphangiogenesis of human lymphatic endothelial cells in vitro, suggested potential role of HMGB1 in lymphatic metastasis of HCC.48,49

Potential Uses of HMGB1 in HCC Treatment

Targeting HMGB1 production or release might be potential approaches for HCC treatment. HMGB1-neutralizing antibodies, sRAGE and RAGE-HMGB1 blocking strategies, platinum and quercetin may be potential candidates for the treatment strategies of targeting HMGB1 in cancers. Most of the studies focus on in vitro and in vivo experiments with animals, and researches on humans has not been performed, so strategies targeting HMGB1 in tumors need further evaluation. So far, ethyl pyruvate, HMGB1-neutralizing antibodies and recombinant human HMGB1 (rhHMGB1) had been reported in HMGB1 associated therapeutic attempts of HCC in animal models.

Ethyl pyruvate

Ethyl pyruvate is one of the inhibitors, which inhibits the release of TNF and HMGB1 from endotoxin-stimulated macrophages, and septic mice treated with this chemical have significantly decreased circulating levels of HMGB1.50,51 Researches about therapeutic values of this chemical are not only limited in sepsis, but also in many noninfectious inflammatory diseases, such as autoimmunity, ischemia/reperfusion (I/R) injury,52 cancer and trauma. The administration of ethyl pyruvate substantially prevents carcino-gen-induced tumorigenesis in a rat model of carcinogen-induced hepatocarcinogenesis, and interestingly this process does not affect p53-mediated hepatic apoptosis.53 In another study, ethyl pyruvate inhibits proliferation and induces apoptosis of HCC cells through regulation of HMGB1-RAGE pathways both in vitro and in vivo.53
HMGB1-neutralizing antibodies

Administration of anti-HMGB1 antibodies before and shortly after endotoxin exposure increase survival of exposed mice.\(^5\) The response is dose dependent, with a higher survival rate correlating with increased frequency of administration of the anti-HMGB1 antibodies.\(^5,6\) Anti-HMGB1 antibodies inhibit release of TNF-α and IL-6 by blocking extracellular HMGB1 but not by preventing HMGB1 secretion.\(^7\) In a nude mouse liver metastasis model, transfection of HMGB1 facilitates liver metastasis of colon cancer cells (CRC cell line), while anti-HMGB1 antibodies inhibit the metastasis.\(^8,9\)

rh HMGB1

Recombinant human HMGB1 (rhHMGB1) induces human lymphatic endothelial cells proliferation, migration, and tube formation in a dose- and time-dependent manner.\(^10,11\) RhHMGB1 induces a distinct form of cell death in cancer cells, which differs from the known forms of apoptosis, autophagy, and senescence, possibly representing an important novel mechanism of specialized necrosis. It exerts potent cytotoxic effects on malignant tumor cells.\(^9\)

Conclusions and Future Perspectives

Extracellular HMGB1 is a proinflammatory cytokine, which enhances tumor cell migration, affects cell proliferation, promotes the formation and maintenance of inflammatory tumor microenvironment and facilitates the growth of new blood microvessels.\(^12,13\)

HMGB1 links with HCC in the process of its formation and development and correlates with its prognosis. Since increased expression of HMGB1 has been approved in HCC cells and in tumor tissue and serum of HCC patients, and changes of HMGB1 affects growth and migration of HCC cells in vitro, it appears to be a promising therapeutic target in HCC. Inhibition of HMGB1, such as the application of its neutralizing antibody or inhibitor, antisense oligonucleotide or using siRNA to affect its production, could decrease the expression of HMGB1 or prevent the combination of HMGB1 with its receptors, and thus block the downstream effects of this DAMP on HCC cells. However, considering wide nuclear functions of HMGB1, inhibition of its intracellular function may lead to some serious consequences,\(^9,10\) so it remains a challenge for targeting this DAMP properly in the treatment of HCC and other cancers.

Following acute cytotoxic treatments including chemotherapy, radiation therapy, epigenetic drugs, oncolytic viruses, and immunotherapy, stressed/dying cancer cells often release HMGB1 and these released HMGB1 is attributed to be harmful to the remained tumor cells.\(^12\) Application of the released HMGB1 in combination therapy and use of it for assessment of the prognosis of HCC might be promising in future.\(^9,10\)

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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