

Review

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The effect of HMGB1 and RAGE on the clinicopathological and prognostic features of prostate cancer

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How to cite this article: Lv DJ. The effect of HMGB1 and RAGE on the clinicopathological and prognostic features of prostate cancer. *J Transl Genet Genom* 2021;5:414-22. <https://dx.doi.org/10.20517/jtgg.2021.34>

Received: 7 Jul 2021 **First Decision:** 16 Aug 2021 **Revised:** 6 Sep 2021 **Accepted:** 9 Sep 2021 **Published:** 5 Nov 2021

Academic Editor: Sanjay Gupta **Copy Editor:** Yue-Yue Zhang **Production Editor:** Yue-Yue Zhang

Abstract

As a DNA-binding protein, high mobility group box 1 (HMGB1) has been shown to be involved in various biological activities, including transcription regulation, DNA repair, genomic stability, and extracellular signaling. Accumulating evidence indicates that HMGB1 has an important role in biological processes in cancer. Moreover, HMGB1 has been shown to have intracellular and extracellular roles, activating key cancerogenic signaling pathways. The main signal pathway is activated via the interaction of HMGB1 with its receptor, receptor for advanced glycation end-products (RAGE). In addition, overexpression of HMGB1/RAGE occurs in certain types of primary tumors and has been linked to increased metastasis and poorer prognosis. In our previous research, we demonstrated that co-expression of HMGB1 and RAGE is associated with cancer progression and poor patient outcome in prostate cancer (PCa). Together with the recent published evidence, we describe and speculate on the character of the HMGB1/RAGE axis in PCa progression and elaborate on future prospects for the application of potential strategies to target HMGB1 in PCa therapy.

Keywords: High mobility group box 1, receptor for advanced glycation end-products, prostate cancer



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INTRODUCTION

Prostate cancer (PCa) is one of the most frequent human malignancies and is the second leading cause of death by cancer in the western male population^[1]. Currently, prostate-specific antigen (PSA) is a significant marker for diagnosing PCa. Nevertheless, the accuracy and specificity of PSA for predicting PCa are not high enough^[2]. Therefore, it is urgent to identify more effective diagnostic hallmarks and therapeutic targets for PCa.

The high mobility group box 1 (HMGB1) protein is a ubiquitous non-histone component of chromatin that is involved in DNA replication and DNA repair process^[3-6]. It has two main functions depending on the cellular localization, post-translational modification, and context of the cell. In the cell nucleus, HMGB1 functions as a DNA-binding complex to sustain nucleosome structure without sequence specificity and aids in distorting the DNA structure to allow access for repair and transcription proteins^[7,8]. The interactions of HMGB1 with various transcription factors, such as NF- κ B members^[9], p53^[10], and TATA-binding protein^[11], can promote or suppress transcription depending on the cellular context. Owing to its ability to bind distorted/damaged DNA structures, HMGB1 has been reported to be involved in four DNA repair pathways: nucleotide excision repair, base excision repair, mismatch repair, and DNA double-strand break repair^[12].

Interestingly, HMGB1 not only promotes DNA damage recognition but can also increase DNA repair efficiency through direct interactions with DNA repair enzymes^[13]. Besides, HMGB1 can also be subjected to posttranslational modification, which modulates interactions of the proteins with DNA/chromatin and regulates their nuclear translocation and secretion^[6,14]. Accumulating evidence indicates that the role of HMGB1 extends beyond the nucleus, notably its extracellular role in inflammation^[15]. Outside the cell, it can be passively secreted from dying or stressed cells or actively secreted from immune cells, such as activated macrophages, which can function as a danger signal and proinflammatory mediator through interaction with multiple other molecules, including RNA, proteins, lipopolysaccharides, nucleosomes, and several cell surface receptors [e.g., receptor for advanced glycation end product (RAGE), toll-like receptor (TLR) 2, and TLR 4], with RAGE being regarded as a dominant receptor for HMGB1 in tumorigenesis^[5,16]. Extracellular HMGB1/RAGE interactions facilitate tumor proliferation via activation of p44/p42, p38, and SAPK/JNK MAPKs^[17]. Moreover, HMGB1 also acts as a DNA-binding cytokine, which can activate downstream immune responses or facilitate tumorigenesis by inducing inflammation^[4,18-20]. For example, it has been reported that enzalutamide-induced HMGB1 expression facilitates tumor-associated macrophage recruitment and polarization and drives neuroendocrine differentiation via β -catenin stabilization, indicating that HMGB1 may serve as a new treatment for enzalutamide resistance in patients with advanced or metastatic PCa^[21].

There is evidence that the HMGB1/RAGE axis is involved in inflammation-induced carcinogenesis^[22]. RAGE, which belongs to the immunoglobulin superfamily, is a cell surface molecule and multi-ligand transmembranous receptor^[23]. HMGB1 is one of its ligand, and it has been reported to bind RAGE and subsequently activate the mitogen-activated protein kinases in a variety of malignancies, such as colorectal, pancreatic, breast, and oral squamous cell cancer^[24-28]. Recent publications show that targeting RAGE reduced the level of PSA, the downstream target gene of androgen receptor (AR)^[29], indicating that RAGE may play a pivotal role in the regulation of AR in PCa cells. Furthermore, Zhou *et al.*^[30] reported that the HMGB1/TLR4-RAGE/sCLU pathway leads to chemoresistance in human prostate tumor cells by triggering the process of cell death, thus providing a survival advantage to residual viable tumor cells.

Although the upregulation of HMGB1 has been found in several cancers, its role in PCa remains elusive. In addition, our previous study revealed that both HMGB1 and RAGE are highly expressed in PCa tissues and serve as predictive factors for the poor prognosis of PCa patients^[31]. Moreover, we also clarified that the HMGB1/BRG1 interaction was associated with the activation of Akt function, resulting in proliferation and metastasis of PCa^[32]. These results suggest that HMGB1 might be a new prognostic biomarker and therapeutic target for PCa. Here, we summarize the recently published literature to highlight and speculate on the interactions of HMGB1 and RAGE in PCa progression and the possible strategies for the targeted therapy of PCa.

HMGB1 AND RAGE IN THE PROGNOSTIC PREDICTION OF PCA

HMGB1 is reported to be frequently increased in various types of cancer^[33-35]. Similarly, HMGB1 is also identified to be upregulated in PCa^[31,36]. Intriguingly, androgen deprivation caused the secretion of HMGB1 in prostatic stromal cells, which was considered to be correlated with metastatic PCa^[37]. These results support the notion that hormone resistance or metastasis of PCa may be due to androgen deprivation therapy, ultimately increasing the level of HMGB1. Furthermore, He *et al.*^[38] showed in the transgenic adenocarcinoma mouse prostate (TRAMP) model that HMGB1 facilitates the invasion of cancer, and HMGB1 released in serum during cancer progression is associated with severity of clinical pathology.

Overexpression of RAGE and HMGB1 has been observed in PCa. Ishiguro *et al.*^[36] found that the mRNA expression of HMGB1 and its cognate receptor, RAGE, is remarkably higher in primary PCa tissues and hormone-refractory tissues than normal prostate tissues. Kuniyasu *et al.*^[37] described that amphoterin is the major product of the *HMGB1* gene co-expression with RAGE and functions as a promoting factor in metastatic PCa. Further, Li *et al.*^[39] explored the relationship of HMGB1 expression with the clinicopathological parameters and overall survival of PCa. They also showed that HMGB1 expression is associated with clinical stage (pT), Gleason grade, PSA level, biochemical recurrence, and poor overall survival. Moreover, they revealed that three PCa cells (PC-3, DU145, and LNCaP) had upregulated HMGB1 mRNA and protein compared to non-transformed immortalized prostate cell RWPE-1. Likewise, our previously study highlights and adds to the theme of HMGB1 acting as a biomarker for advanced stages and poor prognosis for PCa^[31,32]. All these preclinical and clinical studies greatly exhibited that HMGB1 may play a crucial role in the progression of PCa. In addition, research in other laboratories has also shown that members of HMGB1 are consistently increased in different types of human malignancies, including renal cell carcinoma^[33], bladder cancer^[40], hepatocellular carcinoma^[19], gastric cancer^[41], colorectal cancer^[42], breast cancer^[43], and lung cancer^[44]. Thus, it would be interesting to survey tumor samples to further examine the incidence of the abnormal expression of HMGB1 and RAGE in other types of tumors. This systematic analysis would be helpful to determine whether HMGB1 can serve as a reliable biomarker for prostate or other type of cancers.

HMGB1 AND RAGE INTERACTING IN PCA

Growing evidence shows that chronic inflammation is one of the etiological factors of PCa^[45-48]. The HMGB1/RAGE inflammatory pathway promotes growth of tumor cells^[49]. The interactions of HMGB1 and RAGE have been implicated in various types of cancer including PCa^[30]. Zhou *et al.*^[30] showed that the HMGB1/TLR-4/RAGE pathway promotes cell survival via sCLU induction in human prostate tumor cells. However, the specific roles of HMGB1 in PCa are related to its different locations. It has been reported that extracellular HMGB1 has an entirely different role, functioning as one of the damage-associated molecular patterns or alarmin to activate the innate immune system either alone or in conjunction with cytokines or bound DNA^[50]. In the extracellular environment, RAGE binds a downstream domain of HMGB1 at residues 150-183, which regulates chemotaxis, growth, and differentiation in epithelial cells^[51]. HMGB1 combines

with RAGE receptor in PCa cells, and blockade of the RAGE/HMGB1 interaction may suppress tumor proliferation^[52]. This notion is also validated by our recent works^[53], which revealed that the depletion of RAGE by siRNA attenuated the proliferation of PCa cells. Our previous study demonstrated that both RAGE and HMGB1 are co-expressed in PCa specimens, indicating that they may have a cooperative role in the development of PCa^[31]. More recently, Shetty *et al.*^[54] documented that HMGB1 is one of the target pro-inflammatory genes for 18 α -glycyrrhetic acid in PCa cells. Hence, a potential mechanism of HMGB1 in promoting the multistep process of PCa development may be associated with the activation of inflammation, and RNAi-based approaches targeting HMGB1/RAGE may act as a novel therapy for PCa.

Most deaths in PCa patients are attributed to the transactivation of AR, which is required for PCa survival and progression^[55,56]. Recent emerging evidence points out that HMGB1 can transactivate the sex steroid hormone receptors including AR, mineralocorticoid receptor, progesterone receptor, and glucocorticoid receptor^[57,58]. The transactivation of AR by HMGB1 in PCa may have clinical significance^[37]. AR activation suggests it has an action on endocrine glands responding to androgen stimulation. Moreover, AR activation is also known to have a crucial role in the progression of androgen-independent PCa^[59]. The activation of AR is regulated by various signaling pathways^[60]. Thus, these studies indicate that HMGB1 may mediate AR by either acting as co-activator of AR or binding to RAGE in prostate oncogenesis [Figure 1A].

HMGB1 A POTENTIAL TARGET FOR PCA TREATMENT

HMGB1 is implicated as a late mediator for various human diseases including atherosclerosis, sepsis, inflammation, and arthritis^[16,61-63]. Much evidence shows that HMGB1 can also act as a therapeutic target for various tumor types including PCa^[64]. Furthermore, multiple HMGB1 functions have been identified in different types of tumors, including limitless proliferation potential, escape of apoptosis, angiogenesis, inflammatory microenvironment, and tumor invasion and metastasis. Moreover, HMGB1 has been recently shown to regulate most of the key cell signaling pathways, including NF- κ B, p38, JNK, and p44/42 MAPKs, which can be triggered by interacting with RAGE and result in cancer progression and metastasis^[44,65,66]. Hence, identification of the potential HMGB1 targeting strategies is of functional significance in inhibiting the tumorigenesis of PCa.

Antisense and RNA interference (RNAi) techniques are the most used strategies to silence the expression of target genes^[67]. Gnanasekar *et al.*^[52] demonstrated that silencing of HMGB1 by RNAi significantly suppressed cell growth and decreased the number of cells undergoing apoptosis. Furthermore, they also suggested that targeting RAGE by RNAi inhibited HMGB1-mediated cell proliferation of PCa cells and reduced the secretion of HMGB1^[52]. Moreover, Kang *et al.*^[49] demonstrated that knockdown of RAGE or suppression of HMGB1 release by RNAi diminished ATP production and decreased tumor growth *in vitro* and *in vivo*. This growth inhibition phenomenon was also demonstrated in androgen-dependent and -independent PCa in xenograft nude mice. In this case, the RNAi strategies that targeted HMGB1 might be a desirable approach to reach therapeutic effects against PCa.

Antibody-based treatment is a promising strategy for targeted cancer therapy. For instance, anti-PD1 antibody treatment has yielded encouraging results in clinical trials^[68]. In addition, VEGF mAb therapy targeting the angiogenesis process of tumor growth has also been applied^[69]. Thus, HMGB1 may be a promising therapeutic target for PCa, as it is implicated in cell proliferation, apoptosis regulation, angiogenesis, and metastases^[64,70]. He *et al.*^[38] found that administration of anti-HMGB1 dramatically suppressed the prostate tumor growth in TRAMP mouse model. The potential inhibition effect of colon cancer development by anti-HMGB1 has also been reported^[71]. More recently, it was revealed that treatment with anti-HMGB1 neutralizing antibody prevented angiogenesis in colon cancer^[72]. Furthermore, targeting

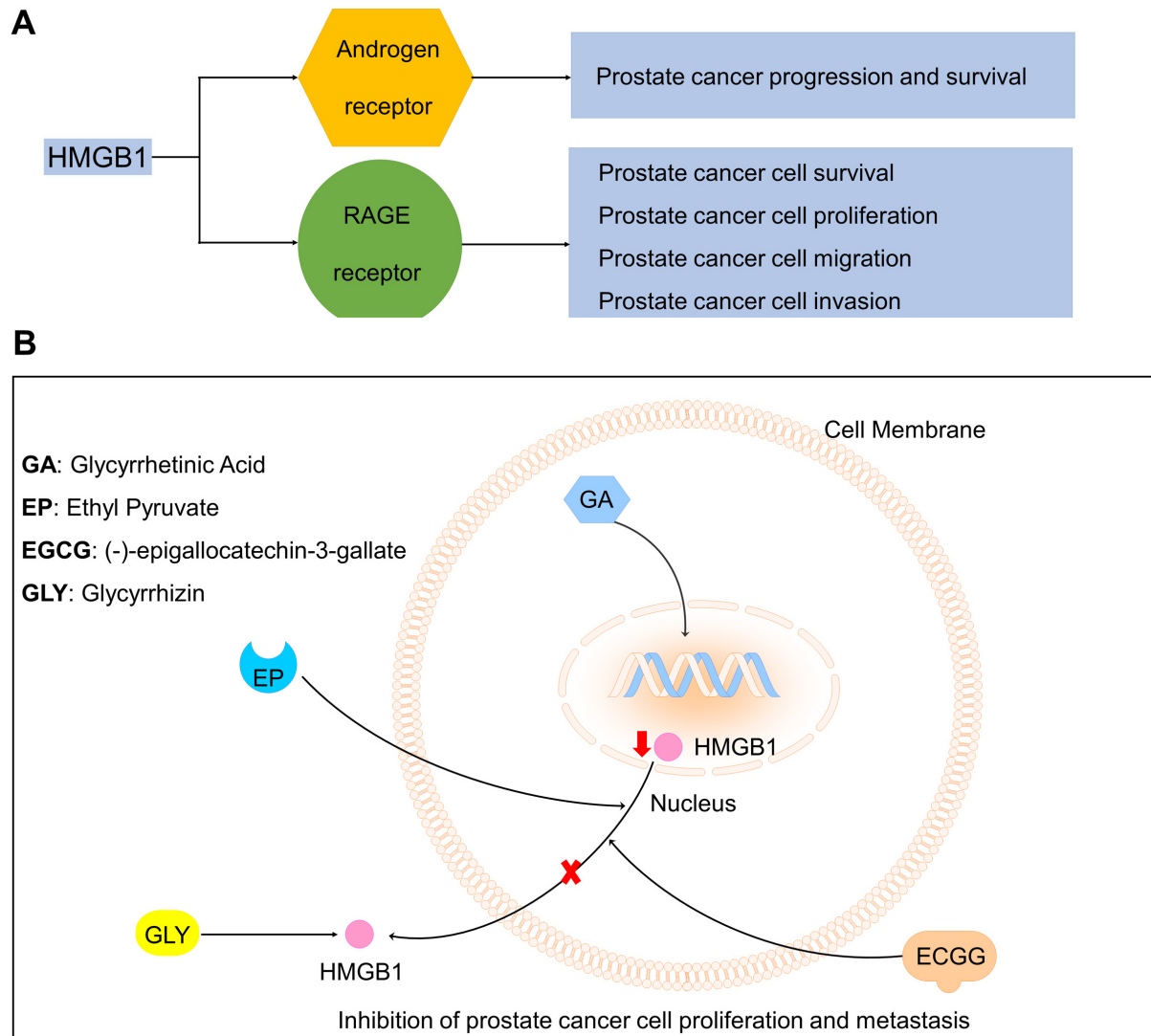


Figure 1. (A) Cellular outcome of HMGB1 interactions with receptors. (B) Hypothetical mode of action of HMGB1 inhibitors.

HMGB1 by antibody was also confirmed to effectively suppress the tumor progression in malignant mesothelioma *in vitro* and *in vivo*^[73]. In summary, these studies proved the curative utility of anti-HMGB1 antibody for cancer treatment generally, which may also be applied for PCa treatment.

The utilization of naturally occurring compounds such as glycyrrhizin, glycyrrhetic acid, ethyl pyruvate, and green tea phenols, especially (-)-epigallocatechin-3-gallate [Figure 1B], may be another promising approach for HMGB1 targeted therapy, as all of these products have been proved to work against HMGB1 in various cell/disease models^[54,74,75]. Specifically, Shetty *et al.*^[54] demonstrated that 18-alpha glycyrrhetic acid, a derivative of glycyrrhizin that is sufficiently expressed in the licorice root, can reduce the expression of HMGB1 and lead to the curative effects in PCa cells. Other natural compounds known to target HMGB1 include some cholinergic agonists^[76], thrombomodulin^[77], and low molecular-weight heparin^[78]. All these natural agents could be tested in PCa patients who show high levels of HMGB1.

Furthermore, the targeting HMGB1 in clinical trials has been carried out vigorously. Several clinical studies have shown that HMGB1 is a promising biomarker for a variety of cancer types. For example, HMGB1 was reported to link hepatocyte injury to ductular reactions, hepatocyte metaplasia, and hepatocarcinogenesis^[79]. The release of HMGB1 in response to proapoptotic glioma killing strategies exhibited high efficacy and safety profile because its blockade with glycyrrhizin completely blocked tumor regression^[80]. These clinical trials could lead to exploring potential cure strategies for cancers harboring high levels of HMGB1 expression including PCa.

CONCLUSION

From recent studies, evidence on the prominent functions of HMGB1 in the development of cancer is rapidly accumulating. Studies from others and our group indicate that HMGB1 may also play a crucial role in PCa progression. The interaction of HMGB1 with RAGE indicates a central role of HMGB1 in PCa progression. Preclinical studies also support that HMGB1 is upregulated in PCa patients and potentially acts as a novel prognostic biomarker for overall survival of PCa patients. Importantly, identification of the molecules that control the status of HMGB1 would both add to the understanding of the regulation role of HMGB1 and potentially provide additional targeted approaches for the therapeutic manipulation of HMGB1, which may ultimately lead to the improvement of effective therapy for PCa patients. In addition, combining hormonal therapy with agents which target HMGB1 may provide novel avenues for therapeutic development against PCa. Nevertheless, further advanced analysis of HMGB1 and elucidation of the complicity of the intracellular and extracellular roles of HMGB1 will give us with the knowledge to further improve the development of effective HMGB1-related anti-cancer therapies. Being easily accessible from body serum, HMGB1 has great potential to become a promising and viable tool for early diagnosis and targeted therapy of cancer.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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