

# Journal of Oncology Research Forecast

## Targeting HMGB-1 in Cancer and Immunomodulation with Vitamin D: Time to Focus and Research

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### Abstract

The failing immunity and chronic inflammatory disease have been acknowledged to contribute to the cancer development. HMGB-1 is a mediator of inflammation and has a paradoxical role in the pathogenesis of cancer. Vitamin D deficiency has been associated with the higher prevalence of cancer and vitamin D supplementation has been associated with decreased cancer. Vitamin D supplementation also decreases inflammation as well as the secretion and expression of mediators of inflammation including HMGB-1. Studies have documented the role of HMGB-1 in cancer development and the role of vitamin D in cancer prevention and treating inflammation, however, the studies discussing the effect of vitamin D on HMGB-1 in the perspective of cancer biology are limited and is the need of the time.

**Keywords:** HMGB-1; Cancer; Vitamin D

### HMGB-1, Vitamin D and Cancer

The crosstalk between the human carcinoma, inflammation, vitamin D, and vitamin D receptor have been discussed in literature. However, the exact mechanism of the immunomodulatory effect of vitamin D on the mediators of inflammation or carcinogenesis involved in the pathogenesis has not been well understood and is an interesting area of research [1,2]. The pathognomonic role of vitamin D in cancer is based on the epidemiological studies suggesting higher incidence, prevalence, and death rates due to cancer in the individuals living in northern latitudes compared to the individual living in southern latitudes having more exposure to light and levels of vitamin D. Studies have also suggested that lower levels of vitamin D are associated with increased risk of cancer and higher vitamin D intakes or higher blood levels of vitamin D have lower risks of specific cancers. However, the results of these studies remained inconsistent [3].

Immunocompromised state or failing immunity has acknowledged as a cause of development and progression of cancer. Thus, targeting the immune system and immune cells to potentiate the immune system for destroying the cancer cells seems promising approach for the cancer treatment. This aspect of treating the cancer by targeting the immune cells to potentiate the immune system comprises of immunotherapy [4]. The current forefront of novel cancer therapy consists of immunotherapy and there is an ongoing need for identification of novel molecular biomarkers and targets [5]. Vitamin D, an immunomodulator agent, may serve as therapeutic agent in increasing the immunity. The role of vitamin D as an immunomodulatory agent to potentiate the immune system has been documented and described in the literature [6-8]. Since vitamin D also acts as an anti-inflammatory agent and inflammation and the polymorphism of receptor for vitamin D [1] plays a crucial role in the pathogenesis of cancer; targeting the mediators of inflammation with vitamin D may be fruitful. High-mobility group box (HMGB)-1, a mediator of inflammation, plays a crucial role in the pathogenesis of cancer, and vitamin D inhibits the secretion of HMGB-1 [9].

High-mobility group box (HMGB) proteins are ubiquitous and abundant non-histone nuclear chromosomal proteins expressed and present in virtually all human cell types [10]. HMGB plays a critical role stabilizing the DNA by binding to distorted DNA structures and regulates transcription, replication, repair, and recombination of DNA. HMGB proteins have two isoforms namely HMGB-1 and HMGB-2 [11]. HMGB-1 is released from the cell actively during cellular stress such as hypoxia, apoptosis and passively during necrosis of cells [12]. Extracellular HMGB-1 through its receptors RAGE (receptor for advanced glycation end-products) and TLRs (toll-like receptors) plays an inflammatory role via activation of downstream signaling involving nuclear factor kappa beta (NF-κB) resulting the release of proinflammatory cytokines. The pathophysiological role of HMGB-1 has been discussed in various inflammatory diseases such as atherosclerosis, osteoarthritis,

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**Received Date:** 26 Apr 2018

**Accepted Date:** 25 May 2018

**Published Date:** 30 May 2018

**Citation:** Rai V. Targeting HMGB-1 in Cancer and Immunomodulation with Vitamin D: Time to Focus and Research. *J Oncol Res Forecast.* 2018; 1(2): 1008.

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cardiomyopathies, chronic obstructive pulmonary disease (COPD), and diabetes to name a few [13-15]. Increased expression of HMGB-1 has been associated with many human cancers such as breast, prostate, pancreatic, and gastric cancer and is closely related to the tumorigenesis and poor prognosis [16-18].

HMGB-1 released during cancer development or while administering the therapeutic agents including chemotherapy, radiation, epigenetic drugs, oncolytic viruses, or immunotherapy may either promote or limit the growth of the cancer. This depends on the state of progression and vascularization of the tumor. The extracellular form of HMGB-1 promotes persistence of surviving cancer cells and enhances autophagy [19] while intracellular HMGB-1 acts as tumor-suppressor [20]. Kang et al. [20] suggest that intracellular HMGB-1 acts as tumor suppressor and thus to decrease or prevent the development of the tumor, the release of HMGB-1 in the cytoplasm or the interaction of HMGB-1 with its receptor on the cytoplasmic membrane should be prevented. Thus, HMGB-1 plays a paradoxical role in promoting both cell survival and death during the tumor development and cancer therapy. The mechanistic aspects and oncogenic and tumor-suppressive roles of HMGB-1 by regulating multiple signaling pathways involved in cancer pathogenesis, including genome stability, immunity, inflammation, proliferation, metastasis, metabolism, apoptosis, and autophagy have been reviewed by Kang et al. [21].

This suggests that HMGB-1 plays a crucial role in the pathogenesis of cancer and may also act as tumor suppressor. Since inflammation plays a crucial role in the pathogenesis of development of cancer and chronic inflammatory diseases increases the risk of cancer development. The complex interaction and interplay between HMGB-1 and various mediators of inflammation such as toll-like receptors (TLRs), triggering receptor expressed on myeloid cells (TREM)-1, and receptor for advanced glycation end products (RAGE), cytokines including interleukins (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , IL-1 $\alpha$ , and IL-1 $\beta$  as discussed in the literature, offers novel therapeutic targets [2,22]. The interaction between HMGB-1 and these mediators of inflammation and the suppressive effect of vitamin D on these mediators has been well described in cardiovascular diseases and osteoarthritis [23-25]. However, the role of vitamin D on these mediators of inflammation, particularly HMGB-1, and the possibilities of targeting HMGB-1 in cancer has not been studied well. Since HMGB-1 plays a crucial role in the development of the tumor and vitamin D has a preventive effect on cancer, the role of vitamin D on HMGB-1 in the perspective of cancer biology should be investigated.

## Conclusion

The studies discussed above suggest that inflammation (HMGB-1) plays a crucial role in the pathogenesis of cancer development and vitamin D suppresses the release of HMGB-1. Extracellular HMGB-1 acts as mediator of inflammation and intracellular HMGB-1 acts as a tumor suppressor. Further, higher levels of HMGB-1 have been associated with the poor prognosis [26]. Thus, HMGB-1 may serve as a novel biomarker and therapeutic target for the treatment of cancer and there is a need of future research.

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