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REVIEW ARTICLE

Role of High Mobility Group Box1 in Pathogenesis of Hepatitis C Virus induced Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma "HCC" is a leading cause of cancer mortality worldwide. High-mobility group box 1 "HMGB1" is a nuclear DNA-binding protein which involved in DNA stability, programmed cell death, immune response and inflammatory responses in HCV and HCC. Its over expression was revealed in HCC and different types of human cancers.

INTRODUCTION

Hepatocellular carcinoma "HCC" is a global health problem with epidemiological variation from place to place. It occupies the 4th place in the most popular cancers in Egypt. Its pathogenesis is contributed to many factors, i.e., persistent intake of alcohol, ingestion of aflatoxin and chronic Hepatitis viral infections which are considered the main causative elements in Egypt. [1]

High-mobility group box 1 "HMGB1" is a DNA binding protein that presents in almost all of nucleated "eukaryotic cells". The average cell has up to 10^6 HMGB1 molecules. It binds in a loose manner to the chromatin and released to the extracellular environment after exposure to various stimulation. Its release causes several pathologies, e.g., chronic inflammation, autoimmune abnormalities, sepsis, chronic renal affection, myocardial infarction and different tumors.[2]

Persistent viral hepatitis causes release "HMGB1" from affected hepatocytes. The interaction of extracellular "HMGB1" with its cellular receptors may activate NF-$_k$B pathways and caspase-1, inducing the elevation of inflammation inducing cytokines like TNF-α, IL-6, IL-1b and IL-18. This causes a continuous inflammation, fibrosis, cellular dysplasia of hepatocytes, angiopoiesis and hepatic tumors at last. [3]

Cheng et al. [4] found significantly elevated serum level of HMGB1among HCC cases compared to cases with chronic cirrhosis and control. This elevated sHMGB1 was in correlation with bad prognosis. In addition Zhou et al.[5] found a correlation between higher serum HMGB1 level and larger tumor and worse stages.

High Mobility Group protein:

High mobility group "HMG" family was discovered for the first time in mammalian cells in 1973. It was named so as a consequence of their high mobility showed on polyacrylamide gels. It weighed about 25 kilodalton (kDa) but migrated to 30 kDa position on the polyacrylamide gel and that might be attributed to the high number of positive charged amino acids [6,7].

HMG is an architectural chromatin-binding factor. It is attached to the minor groove of B-DNA and involved in preservation of nucleosome structure and maintaining the genomic stability. [8]

HMG proteins include three families: HMG-A (HMGA1 & HMGA2), HMG-N which divided from HMGN1 to HMGN4, and the largest HMG-box group, that subdivided into four subgroups; HMGB1, HMGB2, HMGB3 and HMGB4 proteins. HMGB group plays essential roles in recognition and maintenance of DNA in DNA-dependent cellular processes. [9]

High Mobility Group Box 1 "HMGB1" Structure:

"HMGB1" is a very preserved protein of 215 amino acids length. Its encoded gene placed on human chromosome 13. It is consisting of three domains (A, B and C domains). "Box-A" and "Box-B" are proximal homologous DNA binding domains. Both are positive charged (basic in nature) and have nearly the same number of amino acids (~80 amino acids). The 3rd terminal C domain consists of about 30 amino acids. It is negative charged tail (acidic in nature) as the result of aspartate and glutamate amino acid (Figure: 1) [10].

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"Box-A" domain possess an anti-inflammatory characters. It interacts with p53 via 7–74 residues. The "Box- B" was known as a "function domain"; that interacts with TLR4 and RAGE via residues 89–108 and residues 150–183 respectively. This resulted in the secretion of inflammation inducing cytokines.[11]

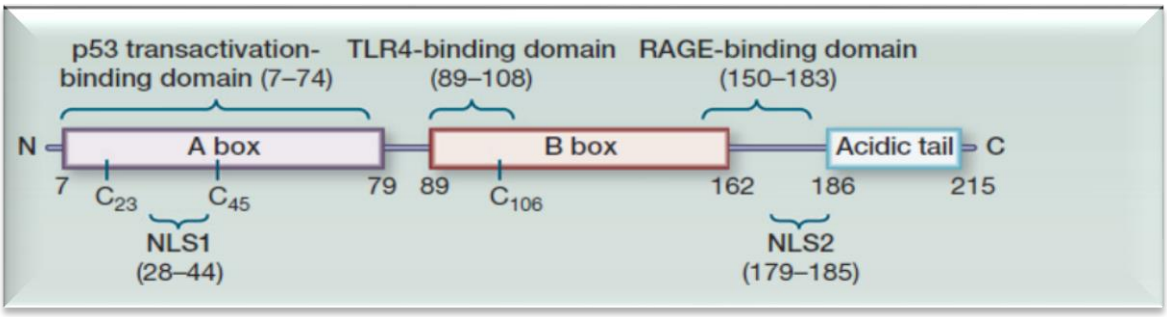

Fig. 1: Structure and binding domains of HMGB1.[10]

Two nuclear localization signals (NLSs) are found to regulate "HMGB1" nuclear transport. They are placed within "Box-A" in positions 28-44 (NLS1) and within "Box-B" in positions 179-185 (NLS2). Intramolecular disulfide bond can be formed between cysteine residues (C_{23}, C_{45}) within "Box-A", also, C_{106} within "Box-B" aids in the interaction with TLR4. These cysteine residues play vital role in HMGB1 activity. [10]

Expression and subcellular localization:

Under normal physiologic conditions, the two NLSs are responsible for placement of "HMGB1" in the nucleus. However, this localization and expression differs according to cell types, stages of development, aging and injury [8].

In normal conditions, high nuclear expression of "HMGB1" was observed in hepatic cells in contrast to lower cytoplasmic expression. Excitingly, some hepatic cells showed major drop of nuclear "HMGB1" or even complete absence. [12]

"Amphoterin" is the expressed "HMGB1" on the plasma membrane of some cells. It was involved in neurons development, metastasis of cancerous cell and chemotactic activity. [13]

"HMGB1" showed elevated cytoplasmic and nuclear expression in the spleen, testis and other lymphoid organs. Moreover, low cytoplasmic expression in adult brain, while higher nuclear, cytoplasmic and plasma membrane expression in Peripheral nervous system was observed [14].

Earlier studies revealed the extremely elevated expression of "HMGB1" in tumor tissues compared to the normal ones, i.e., cancer breast, colorectal carcinomas and HCC[15]. While, no "HMGB1" was revealed in some types of cancers as adrenal gland carcinoma [8].

HMGB1 release:

Hyper acetylation of lysine residues located in NLS1 (28-30) and NLS2 (180, 182-185) encourages cytoplasmic transfer of "HMGB1", prevents its nuclear re-entery and HMGB1 release.[10]

HMGB1 constantly shuttles bi-directionally between the nucleus and the cytoplasm as the result of importin and exportin action**.** It can be sliced by thrombin and thrombo-modulin between arginine amino acid and glycine amino acid at 10^{th} and 11^{th} position. Also, caspase-1 cleaves at 67^{th} position (aspartate amino acid) and 68^{th} position (lysine amino acid). It was unknown, whether caspase-1 cleavage aids in prevention of "HMGB1" nuclear re-entry or in participation in protein degradation or even instability**.** [16]

"HMGB"1 also called the "leaderless" cytokine; due to the deficiency of the conventional hydrophobic leader secretion signal peptide. It needs specialized means to reach the immunological synapse or to be secreted in endolysosomal organelles.[18] Extracellular "HMGB"1 is released either passively; from the dead cells or injured ones, or actively from cells of innate immunity, e.g., monocytes [13].

HMGB1 receptors and its extracellular role:

Binding of extracellular "HMGB1" to its receptors causes activation of different signaling pathways, e.g. phosphoinositide 3-kinase (PI3K), NF-κB and IFN regulatory factor-3 (IRF3). These signals activate cells of innate immunity, stimulate release of type I IFNs and pro-inflammatory cytokines, stimulate cell proliferation, promotion angiogenesis, inhibit the phagocytosis process and increase autophagy. [17]

"HMGB1" binds to several receptors, e.g., RAGE, TLR (2,4 and 9), T-cell immunoglobulin mucin- 3 (TIM-3), CD24, phosphacan protein- tyrosine phosphatase (PPTP) and C-X-C chemokine receptor type 4 (CXCR4) (Figure: 2)[18]. TIM-3 and CD24 receptors are considered negative receptors that inhibit HMGB1 immunogenic activity in tumor-associated dendritic cells and macrophages correspondingly. [19]

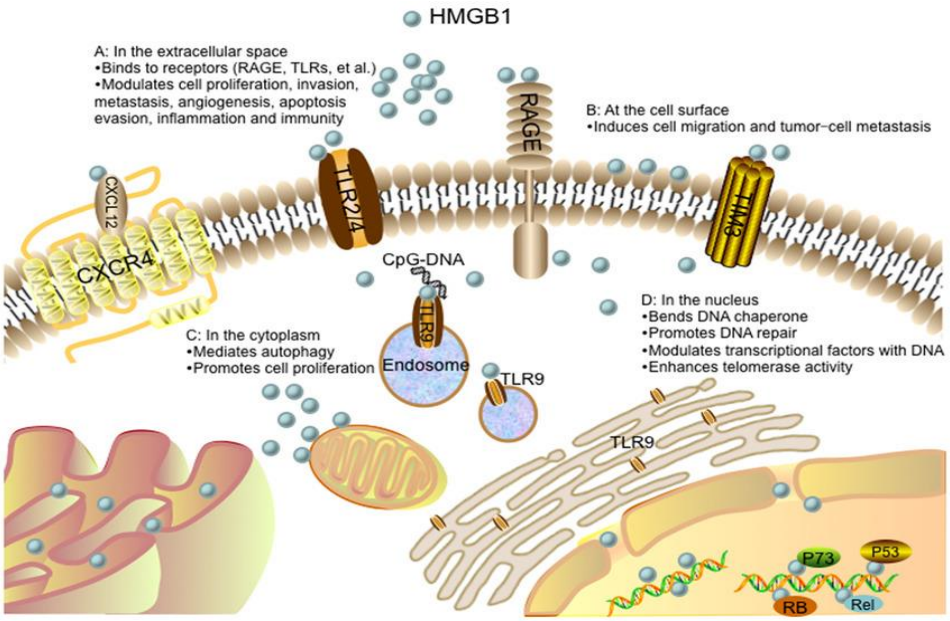

Fig. 2: Receptors and roles of HMGB1 extracellular, cytoplasmic, at cell surface and nuclear[18]

a) Receptor for advanced glycation end products "RAGE":

RAGE binds to "HMGB1" with a strong affinity. This interaction can stimulate cell survival, growth, chemotaxis, migration, inflammation and autophagy. Also, RAGE binds to different types of ligands, e.g. certain S100 proteins and different molecules to control some physiological and pathological activities.[20]

b) Toll-like receptors "TLRs":

TLRs can interact with multiple damage-associated molecular pattern molecules "DAMPs" as "HMGB1". They are found to exhibit both pro-tumor and anti-tumor functions depending on the different signaling pathways; TLRs promotes the survival and propagation of malignant cells and suppresses the immunity. In contrast, it can improve the immune reactions against tumors besides stimulation of death direct of malignant cell [21].

Dendritic cells expressed TLR4 binds to "HMGB1" released from irradiated malignant cells to activate tumor-specific T cells plus destruction of malignant cells [22].

c) CXCR4:

CXCR4 is greatly expressed in cancerous tissues compared to normal ones. This over expression was in correspondence to higher tumor stage, metastasis and even recurrence. CXCR4 interacts with CXC chemokine ligand 12 "CXCL12" bound to "HMGB1" to recruit the inflammatory cells into the injured tissues. The attraction between CXCR4 and CXCL12 encourages cellular invasion through the stimulation of NF-κB signaling pathway as the chief pathway.[23]

d) TIM3 T cell immunoglobulin domain and mucin domain-3 "TIM3"

"HMGB1" can interact with TIM3 receptor located on DC and repress the endosomal mobilization of nucleic acids. This weakens the antitumor effectiveness of DNA vaccines. Conversely, it was noticed that augmentation of the antitumor effectiveness of cytotoxic drugs occurred after blocking of TIM3 receptor. [19, 24]

Phagocytosis of the apoptotic cells enhanced by phosphatidyl-serine (PtdSer) molecule which binds also to TIM3. So, knocking out TIM3 results in impairment of DCs' phagocytic activity and hindering the removal of dead malignant cells. [19]

HMGB1 and cancer

The significant participation of extracellular "HMGB1"in cancers development and progression was contributed to its cytokine activity that leads to inflammation, angiogenesis, proliferation of cells, invasion and tumor metastasis. Multiple studies had revealed the role of "HMGB1" in the genesis of different cancers. [25]

HMGB1 and hepatocellular carcinoma:

Different studies showed that the serum HMGB1 levels showed significantly higher values in patients with HCC in comparison to patients with chronic hepatitis, liver cirrhosis and healthy controls. It was significantly interrelated to the clinic-pathologic characterizations, e.g., level of alpha-fetoprotein, tumor size, tumor staging, metastasis and outcome. So, it was considered as a predictor of poor clinical state in HCC patients. [5]

Regarding involved receptors, overexpression of RAGE was observed primary hepatic tumor compared

to healthy hepatic samples. It was shown that HMGB1/ RAGE binding promotes HCC proliferation. In hypoxic HCC cells, "HMGB1" activates caspase-1 with the consequent release of multiple inflammatory mediators as IL-1b and IL-18. This encourages cancer progression and distant spread[26].

The tumorigenic role of HMGB1 was studied in mouse models of HCC in response to carcinogens such as diethylnitrosamine and carbon tetrachloride that could induce chronic hepatocyte death, inflammation and fibrosis.[27] Genetic removal of HMGB1 caused delayed tumor progression in autophagy-deficient livers. RAGE co-deletion delayed the tumor development as well, suggesting that HMGB1 can mediate the tumor development via RAGE. [28]

The role of HMGB1 in tumorigenesis could also be mediated by a cell-intrinsic mechanism. In diethylnitrosamine -induced HCC model, HMGB1 was found to transcriptionally regulate the expression of yes-associated protein "YAP", a major downstream effector of the hippo pathway that contributes to liver tumorigenesis by inducing hypoxia-inducible factor 1α dependent aerobic glycolysis. [29]

HMGB1's pro-tumor roles in hepatocarcinogenesis:

HMGB1 role in cell proliferation:

HMGB1 enhances cell proliferation in multiple mechanisms: promoting the cell cycle transition from G0/G1 to S phase or through an autocrine circuit. Also, extracellular HMGB1/RAGE provides adenosine triphosphate "ATP" needed by tumor cells for supporting proliferation[18,30]. HMGB1 was found to increase "cyclin D1" and proliferating cell nuclear antigen"PCNA" which are essential in HCC proliferation.[31]

HMGB1 role in cell differentiation:

Intracellular HMGB1 has also been shown to encourage mitochondrial biogenesis in hypoxic HCC cells. It also stimulates expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) which is a nuclear receptor that controls expression of genes needed for cell differentiation and so, promoting tumor survival and proliferation[32]. RAGE receptors showed higher expression in well and moderately differentiated HCC tissues than poorly differentiated ones. Also, RAGE was found to have higher level in hypoxia resistant HCC cells that significantly prolong cell survival and availability under hypoxic conditions needed for early stages of oncogenesis[33].

HMGB1 role in invasion and metastasis:

HMGB1/RAGE interaction activates mitogen-activated protein kinase (MAPK) or NF-κB signaling pathway. This stimulates matrix metalloproteinases "MMP", such as MMP2 and MMP9 also it represses "MMP" inhibitors. MMPs degrade extracellular matrix proteins and play a major role in tumor spread. [28,34]

HMGB1 role in angiogenesis:

Formation of new blood vessels "Angiogenesis" is vital for the majority of solid tumors and it depends on balance between anti-angiogenic and pro-angiogenic mechanisms in the tumor microenvironments "TME". As soon as released, "HMGB1" triggered secretion of vascular endothelial growth factor (VEGF) mainly through its disulfide form interacting with TLR4."HMGB1" can also aggravate the activation and mobilization of macrophages that secrete angiogenic factors, e.g., TNF-α and IL-8. Subsequently, using "HMGB1" antibody hinders new blood vessels formation; this inhibits development, progression and spread of tumor. [26]

HMGB1 deletion caused a noticeable reduction in DCs expansion, which is characteristic hallmark in hepatocarcinogenesis.[27,35] It was unknown whether HMGB1 mediated DCs expansion could participate as a cellular source for the tumor formation. Alternatively, these DCs could modulate the tumor microenvironment by secreting "VEGF-D", platelet-derived growth factor C "PDGFC" and angiopoietin 1.[36]

HMGB1 and inflammation:

Extracellular HMGB1 induce chronic inflammation inside the TME that encourages tumor growth, proliferation, metastasis and angiogenesis. HMGB1 expression was found to be linked to tumor staging of liver cancer. HMGB1 release inhibitor "Ethyl pyruvate" prevents liver cancer development and metastasis. [37]

"HMGB1" recruits leukocytes and encourage the release inflammatory cytokines such as TNF, IL-1 and IL-6. Tumor-infiltrating leukocytes along with cytokine-related signaling pathways support tumor progression and metastases. Infiltrating leukocytes and cancerous cells are able to secrete "HMGB1" under hypoxia, injury, inflammatory stimuli or environmental factors. [30]

HMGB1 role in apoptosis inhibition:

HMGB1 inhibits both intrinsic and extrinsic pathways of apoptosis in a caspase-dependent way in cancer cells. Extracellular HMGB1 up-regulates transcription of anti-apoptotic member of the Bcl-2 released from myeloid cell leukemia-1. So, tumor cells are protected from apoptosis, In HCC, the translocation of HMGB1 to the cytoplasm was found to inhibit apoptosis and induce autophagic cell death which may be associated with ROS and Beclin1. [38]

HMGB1 as a target for anticancer therapy

Many theories suggested targeting "HMGB1" to inhibit its expression, release or even its activity could be used in treatment of cancer in addition to different inflammatory diseases. Different agents targeting "HMGB1" were tried in different experimental cancer research. These agents classified into 3 levels: a) HMGB1 inhibitors, b) agents targeting HMGB1 receptors and c) inhibitors of HMGB1 secretion (figure: 3).[18]

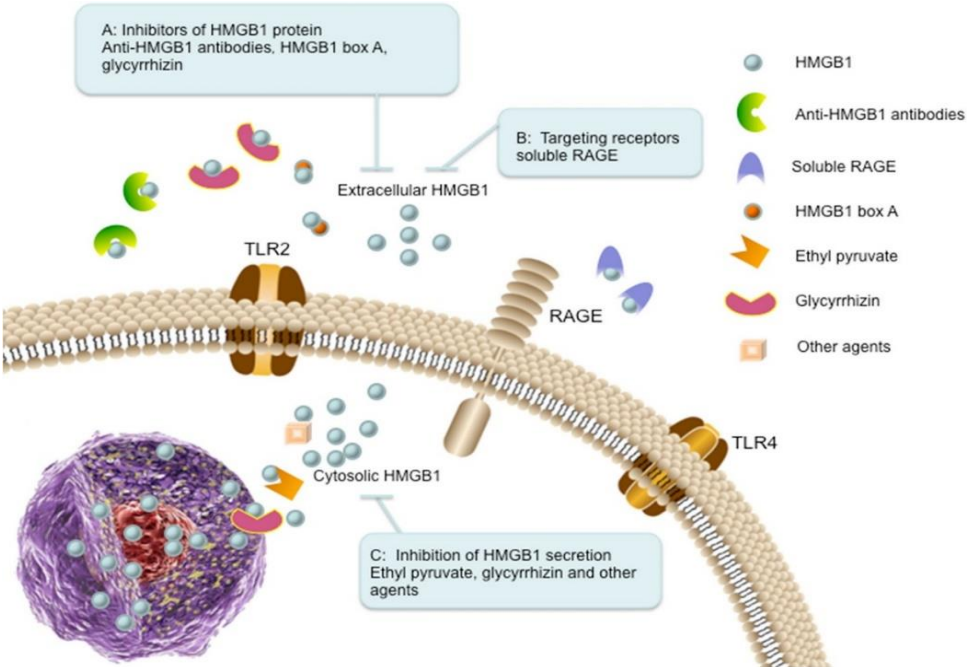

Fig. 3: The therapeutic agents targeting HMGB1 in cancer. (A) HMGB1 Inhibitors **(B)** Targeting receptors. **(C)** Inhibitors of HMGB1 secretion. [18]

Inhibitors of "HMGB1" protein:

"HMGB1" inhibitors include many agents as anti-HMGB1 antibody, neutralizing anti-HMGB1 antibody and HMGB1 "Box-A" protein. It was noticed that anti-HMGB1 antibody in the therapeutic regimen of colorectal carcinoma was able to hinder metastasis to liver tissue. Also, neutralizing anti-HMGB1 antibody was found to decrease the tumorigenic role of extracellular "HMGB1" obtained from resistant breast cancer cells in a significant way. [39]

HMGB1 "Box-A" can be applied to antagonize the "Box-B" functional activity and prevent HMGB1-associated inflammation and tumorgenesis. Antisense oligodeoxynucleic acid technology could be used to knockdown HMGB1 causing inhibition of cancer cell development and metastasis. [34]

Targeting receptors:

Blocking HMGB1/RAGE signaling pathway could be used to prevent growth of malignant cells and its distant metastasis, this was achieved by repressing activation of MAPK, needed for tumor development. A truncated form of RAGE receptor called soluble RAGE "sRAGE" that consists of only the extracellular domain, was administrated to block the HMGB1/RAGE signaling pathway effectively in animal models**.** [18]

Inhibition of "HMGB1" secretion:

Some cancer tissues, e.g., colon cancer and malignant mesothelioma are able to secrete "HMGB1" into the culture media. Inhibition of "HMGB1" secretion could aid in tumor treatment. Platinating substances "cisplatin" was found to keep "HMGB1" inside the nucleus as a result of abnormal changes in the double helix which prevents the stable binding of "HMGB1". Ethyl pyruvate is the first used inhibitor of "HMGB1" release. Also, it suppresses NF-κB activation and RAGE expression. [30]

CONCLUSION

Extracellular HMGB1 acts as a DAMP molecule that trans-locates to the cytoplasm under oxidative stress condition. It interacts with many receptors and activates NF-$_k$B pathways and caspase-1, inducing the elevation of inflammation inducing cytokines like TNF-α IL-6, IL-1b and IL-18. This causes a continuous inflammation, fibrosis, cellular dysplasia of hepatocytes, angiopoiesis and lastly HCC.

Conflicts of interest:

The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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