Role of High Mobility Group Box 1 Protein in Pulmonary Arterial Hypertension and Different diseases

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Abstract

High-mobility group box 1 protein (HMGB1) is a highly conserved nuclear protein that has a surprising extracellular role. Not only does it bind DNA, increasing access to transcription factors, but it also recruits cells across endothelial barriers and promotes the local production of tumour-necrosis factor (TNF), interleukin-6 (IL-6) and interferon-γ. Controlling HMGB1 activity and release is an approach that is being developed as an experimental therapy for patients with sepsis, arthritis, cancer, PAH and other disorders.

KeyWords:HMGB1, PAH, hypertension.

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Introduction.

Previous studies reported on the critical role of high mobility group box-1 (HMGB1) in inflammation and immune response (Kang et al., 2014). HMGB1 is a nuclear protein and danger-associate molecular pattern molecule (DAMP) constitutively expressed in most cells. Under physiologic conditions, it acts as a structural component in the chromatin complex, shaping nucleosomal structure and influencing multiple processes in the chromatin. However, in response to cellular stress, numerous immune and non-immune cells release HMGB1 into the extracellular space where it acts as a DAMP. Recently,two studies indicated that HMGB1 plays a role in the pathologic processes of PAH and elevated serumHMGB1 level was observed in patients with PAH**(1)**.

Inflammation, vasoconstriction and proliferation of smooth muscle, endothelial cell dysfunction, and thrombosis formation are thought the major mechanisms contributing to the pathophysiology of PAH **(2).**

A growing number of biomarkers associated with the three major mechanisms have been evaluated for diagnosis and evaluation of PAH **(3).**

The inflammatory response rapidly stimulate immune cells by recruiting multiple cytokines and chemokines and upregulating adhesion molecule expression (**4**). In particular,injured cells release danger-associated molecular patterns (DAMPs) that induce or escalate inflammation **(5).** These DAMPs include high-mobility group box-1 (HMGB1)**(6)**. HMGB1 is

a nuclear protein with proinflammatory activity in sepsis and ischemia **(7)**.

Under ischemic conditions, HMGB1 is passively released from necrotic cells and actively secreted by stimulated inflammatory cells. **(8).** Once released, HMGB1 acquires proinflammatoryactivity and acts as a DAMP **(9).**

HMGB1 is a protein that is expressed in various cell types, and its presence in the nucleus is required for transcriptional regulation and gene expression **(10)**. Various stimuli favor its release from the cell whether by a passive or active mechanism **(11).**

It is increased in inflammatory processes such as severe Acute Pancreatitis, sepsis, mechanical trauma, acute myocardial infarction, and rheumatoid arthritis **(12).**

In the extracellular space,HMGB1 binds to receptors such as RAGE (receptors for advanced glycation end products) and to TLR4 (Toll-like receptor 4), linked to inflammatory processes**(13).**

HMGB1is a late product of endotoxin-stimulated macrophages that can be secreted into the extracellulararea passively or actively through the cytoplasm (**14).**

In the extracellular area, HMGB1 binds to receptors, such as toll-like receptor 2 (TLR2) and TLR4, and transfers inflammatory signals. Therefore, the mechanisms of HMGB1 translocation are considered important for controlling immunologic activity. Recently, oxidative stress has been found to bea critical factor in determining the cytokine function ofHMGB1 **(15)**.

In the extracellular area, HMGB1 functions asa DAMP, also known as alarmin, which signals cellular dam-age and activates the innate immune system **(16).**

HMGB1, a nonchromosomal nuclear protein, could regulate gene transcription and maintain the nucleosome structure **(17).**

HMGB1 was first demonstrated as a delayed mediator in inflammatory responses in sepsis and showed that the inhibition of HMGB1 confers significant protection against the lethal effects of endotoxin, indicating that the extracellular HMGB1 plays a important role in the pathogenesis of sepsis. **(18).**

Functions:

HMGB1 also functioned as a novel pro-inflammatory cytokine in cardiovascular diseases**(19).**

HMGB1 is passively released by necrotic and damaged cells, apoptotic cell or by activated innate immune cells (such as macrophages and monocytes), and functions as a pro-inflammatory cytokine **(17)**.

Once released from necrotic cells, apoptotic cell and macrophages, HMGB1 functions as an inflammatory stimulus that upregulates IL-1, IL-6, TNF, and macrophage inflammatory proteins (MIP-1and MIP-1) **(20).**

Structure:

HMGB1 (high-mobility group box-1), a 30-kDa nuclear and cytosolic protein, is one of the best chracterized damage-associated molecular patterns **(21)**

HMGB1 is expressed in almost all human cells and is released during apoptosis and necrosis, as well as by activated immune cells. The structure of the protein is presented in Figure 1 It consists of 215 amino acid residues comprising three binding domains. Two of these domains are helical deoxyribonucleic acid (DNA)-binding domains consisting of HMG A-Box (9–79 amino acid residues) and HMG B-Box (95–163 amino acid residues) **(22)**

The third domain comprises a shorter acidic C-terminal tail containing a series of glutamic and aspartic acid residues of various lengths (186–215 amino acid residues), which encompass RAGE and TLR binding sites **(23).**

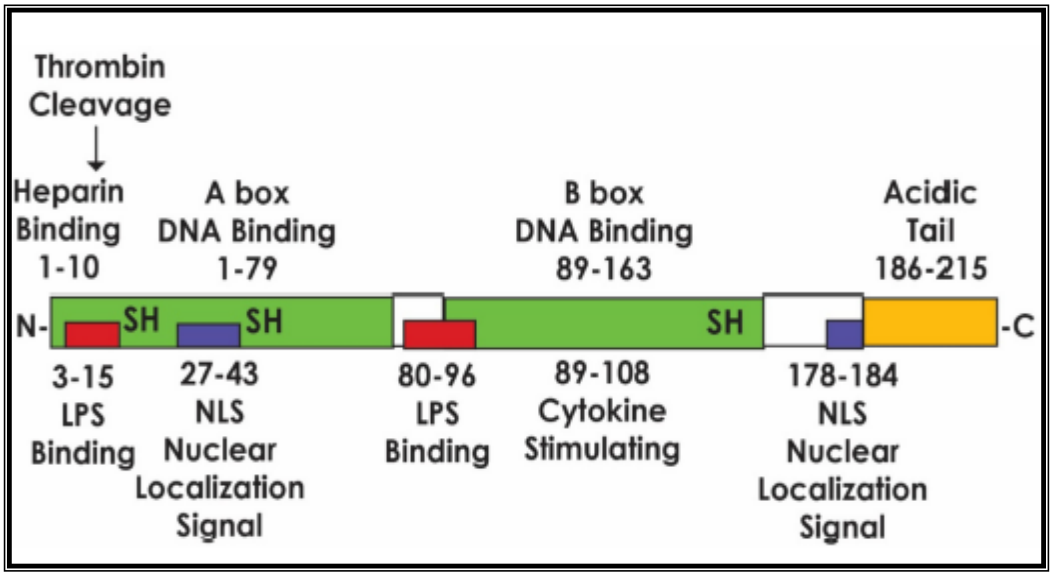

Fig. (1): The structure of High mobility group box protein 1 (HMGB1). The A- and B-box binding moieties are shown. The three cysteines determine whether HMGB1 acts as a proinflammatory mediator when outside the cell or binds to DNA when inside the nucleus. In addition, protein stability and DNA bending in vitro is determined by the C-terminal acidic tail **(24)**

HMGB1 has three conserved cysteines (C) encoded at amino acid positions 23, 45 and 106 . C23 and C45 can form an intermolecular disulfide bond, whereas C106 remains in a reduced thiol state. This allows for three diferent redox forms of HMGB1 namely: (i) all-thiol-HMGB1;(ii) disulfide-HMGB1; and (iii) oxidized HMGB1 **(8).** (Figure 2). The all-thiol isoform, with all three cysteines reduced, is the predominant type of HMGB1 in the nucleus. It is reported to be a chemokine-like molecule **(25).**

The recruited leukocytes then produce disulfide-HMGB1 by oxidizing extracellular HMGB1 via the production of reactive oxygen species (ROS) **(26).**

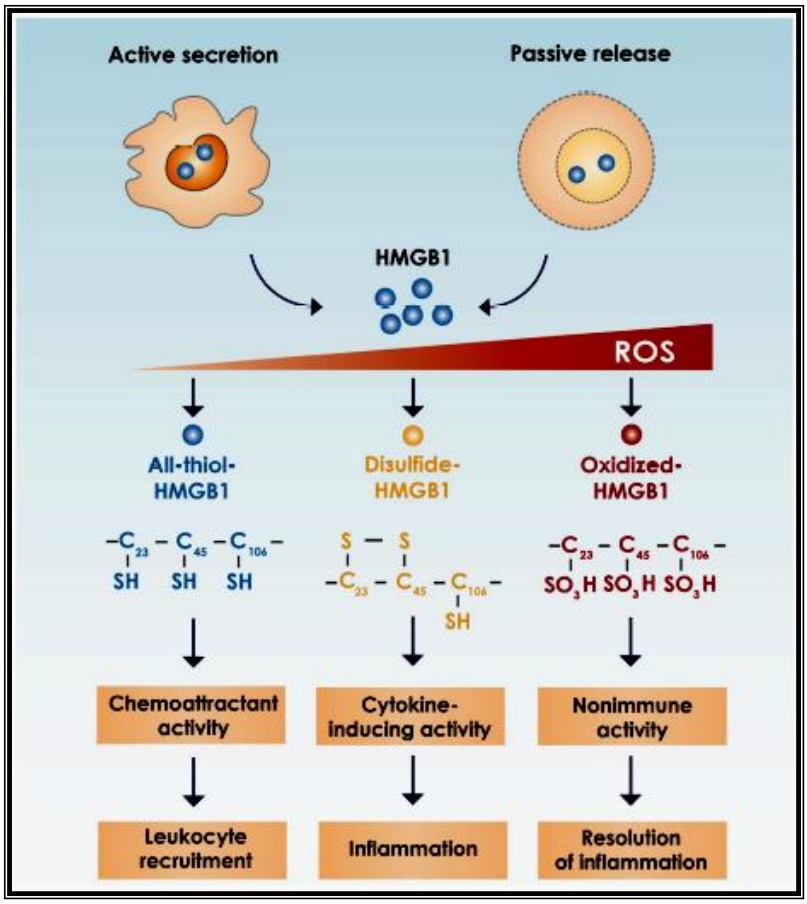

Fig. (2): The redox state of HMGB1 determines the activity of the protein. Chemokine production and leukocyte recruitment are mediated by all-thiol-HMGB1. In turn, disulfide-HMGB1 facilitates the release of proinflammatory cytokines. During resolution of inflammation, reactive oxygen species inactivate HMGB1 by inducing the terminal oxidation of the protein **(8).**

The disulfide form of HMGB1, which is produced a few hours after all-thiol-HMGB1, activates monocytes/macrophages, as well as other cell types, to produce cytokines, chemokines and other inflammatory mediators by binding to TLR2 and TLR4. Binding of disulfide-HMGB1 to TLRs leads to the translocation of nuclear factor kappa-light-chain-enhancer of activated B cells to the nucleus and transcription of pro-inflammatory cytokines such as tumor necrosis factor (TNF) interleukin (IL)-1, IL-6 and IL-8 **(27)** . During inflammation, disulfide-HMGB1 accumulates in the extracellular space.

HMGB1 is also released passively by necrotic or damaged cells during oxidative stress **(28).**

The HMGB1 released by necrotic cells sends a 'danger' signal to neighboring cells by mediating an inflammatory response **(29).**

Function of HMGB1

1. Basic Function of HMGB1 in the Normal Cell: Nuclear and Cytosol Function

The function of HMGB1 is determined by its cellular location. As mentioned, HMBG1 is usually localized in the nucleus and has an important function in maintaining DNA structure through its DNA-binding and bending activities. exhibits pro-inflammatory activities, (**30).** In the nucleus, HMGB1 has been shown to be involved in replication, transcription, chromatin remodeling With respect to its cytoplasmic location, HMGB1

is prevented from relocating to the nucleus in activated monocytes by the acetylation and phosphorylation of the protein, resulting in the accumulation of HMGB1 in the cytoplasm **(31)**. Cytoplasmic HMGB1 is involved in modulating cell stress responses, as well as inhibiting apoptosis via binding to, and protecting, while promoting autophagy and regulating mitochondrial morphology and function (**32).**

Immune Functions of HMGB1

The immune protective and suppressive functions of HMGB1 are covered, HMGB1 exhibits cytokine-like functions by acting as a proinflammatory mediator in immunity when it is secreted into the extracellular matrix. This occurs when the protein is passively released from necrotic cells, or is actively secreted by inflammatory cells such as monocytes, macrophages, natural killer cells, as well as platelets and endothelium following infection and exposure to inflammatory mediators **(33).**

Once outside the cell, HMGB1, by acting as a DAMP, mediates local or systemic immune responses via its interactions with several pattern of recognition receptors include RAGE,TLR2, TLR4**(34)**.

The oxidation state of HMGB1 determines its role as a chemokine or cytokine **(33).**

2. HMGB1 and Lymphoid Cells

T cells are key components of the adaptive immune system and play a critical role in immune responses to self and foreign antigens **(35)**

HMGB1 also acts directly as a proliferative signal for both human CD4+ and CD8+ T cells in response to stimulation with suboptimal levels of anti-CD3

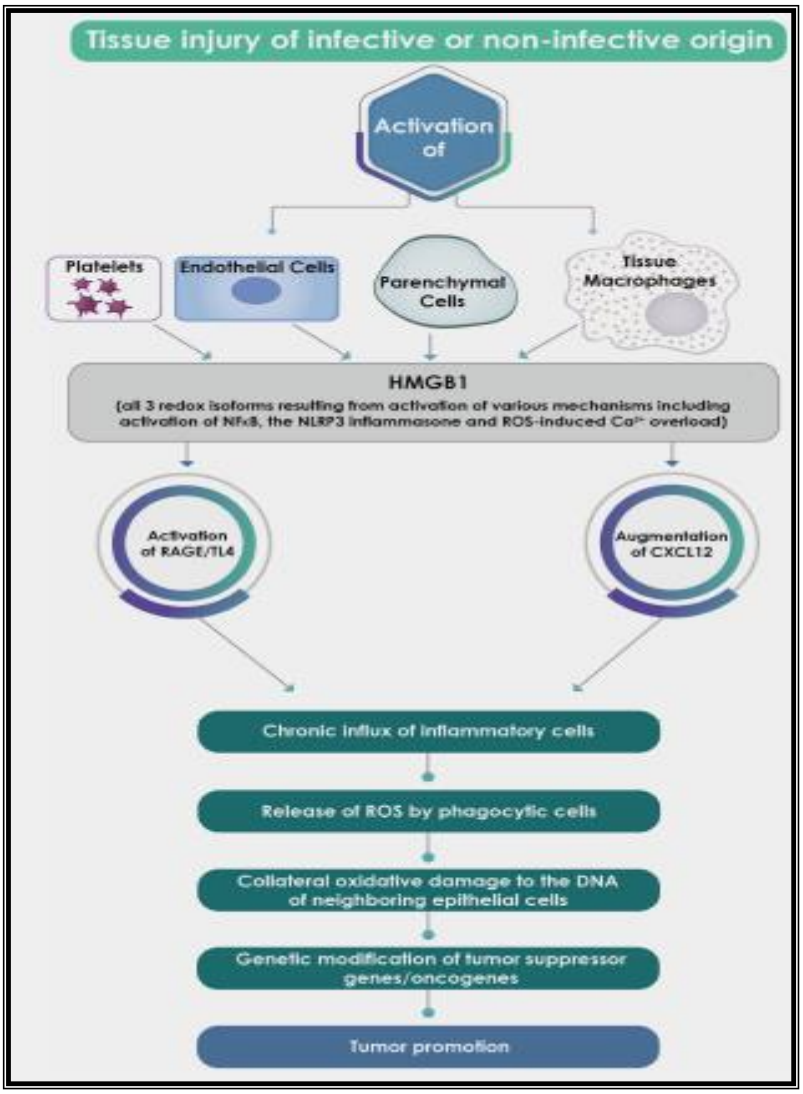

Fig. (3): Summary of events by which HMGB1 derived from endothelial cells, tissue macrophages and parenchymal cells at sites of chronic tissue injury may drive a chronic inflammatory response that potentially leads to the development of epithelial cell injury, oxidative/inflammatory damage to DNA and tumor promotion.**(36).**

Researches about HMGB1in medicine:

- **Tang *et al.*, (37),** who indicates that serum levels of HMGB1 in newborns with PPHN are significantly increased early after PPHN onset, and then decreased after remission, and that they are positively correlated with levels of inflammatory factors
- **Zemskova *et al.*, (38)**, who reported that HMGB1, play a well-recognized role in the development of pulmonary arterial hypertension
- **Fan *et al.*, (39),** who demonstrated significantly higher plasma HMGB1 levels in patients with CHD.
- **Kam *et al.*, (40),** who said that Inhibition of HMGB1 could promote MDS cell death and alter innate immune responses via suppression of NFκB pathways
- **Tsukagawa *et al.*, (21),** who found that serum HMGB1 levels are increased in patients with acute ischemic stroke, and higher levels of this molecule on admission are associated with poor outcomes.

- **Arriaga-Pizano *et al.*, (41)**, who reported that High serum levels of HMGB1 is associated with poor prognosis for patients with Acute Pancreatitis.
- **Min *et al.*, (42)**, who said that the serum HMGB1 level reflects the severity of disease in Obstructive Sleep Apnea patients
- **X. Hu *et al.*, (43),** who found that serum HMGB1 level was markedly increased in paroxysmal and persistent AF patients.
- **Chen *et al.*, (44),** who studied the value of circulating HMGB1 as a clinical biomarker and the development of anti-HMGB1antibodies or antagonists in therapeutics for the targeted prevention, management, and treatment of chronic inflammation, obesity, and CVD.
- **Rapoport *et al.*, (36),** who studied the role of HMGB1in cancer
- **Yamaguchi *et al.*, (45)**, who discovered that HMGB1 is associated with acute deterioration of Idiopathic pulmonary fibrosis
- **Kim *et al.*, (46)**, who provided that the primary evidence of HMGB1 concentration measured 1 h after weaning from CPB is independently associated with adverse outcomes after cardiac surgery
- **Huang *et al.*, (47),** who summarized that HMGB1 had a potential effect on PAH progression in CHD patients, and suggested that serum HMGB1 level may be used as a biomarker to indicate PAH in patients with CHD and to assess the pulmonary vascular remodeling in CHD patients with PAH. **(45).**

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