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Review Article

Post-translational modifications of high mobility group box 1 and cancer

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Abstract: Post-translational modifications (PTMs) of High mobility group box 1 (HMGB1) have not been investigated as extensively as those of other HMG proteins but accumulating evidence has shown the remarkable biological significances induced by the post-translational: acetylation, methylation and phosphorylation, oxidation, glycosylation and ADP-ribosylation of the HMGB1 to modulate its interactions with DNA and other proteins. Although HMGB1 is localized in the nucleus in almost all cells at baseline, it can be rapidly mobilized to other sites within the cell, including the cytoplasm and mitochondria, as well as into the extracellular; hence there is an increasing interest by researches into the complex relationship between the PTMs of HMGB1 protein and its diverse biological activities. The PTMs of HMGB1 could also have effects on gene expression following changes in its DNA-binding properties and in extracellular environment displays immunological activity and could serve as a potential target for new therapy. Our reviewed identifies covalent modifications of HMGB1, and highlighted how these PTMs affect the functions of HMGB1 protein in a variety of cellular and extra cellular processes as well as diseases and therapy.

Keywords: HMGB1, post-translational, modification, cancer, autoimmune disease

Introduction

High mobility group box 1 (HMGB1) is the most abundant and well-studied HMG proteins. It senses and coordinates the cellular stress response and plays a critical role inside the cell as a DNA chaperone, chromosome guardian, autophagy sustainer, and protector from apoptotic cell death [1-3]. HMGB1 can also be designated as a damage- (or death-) associated molecular pattern (DAMP) by analogy to a pathogen-associated molecular pattern (PAMP) because of its origin and immunological properties [4]. While PAMPs are exogenous molecules and DAMPs are endogenous molecules, they both responses to physiological and pathological events via interacting with cellular receptors such as the Toll-like receptors (TLRs) as well as induction of similar downstream signaling events. HMGB1 is also the most mobile protein in the nucleus and has the ability translocate into the cytosol within 1-2 seconds [3, 5]. Because of the translocational ability of HMGB1, it can be found in the cytosol e.g., mitochondria [6] and lysosome [7]. Furthermore, in the cellular membrane, and extracellular space its nuclear localization signal (NLS) can be modified. Nevertheless, the subcellular location of HMGB1 changes depending on cell type, tissue, and stress signals.

HMGB1 is also a non-histone nuclear protein with multiple functions; it interacts with DNA to modify its structure and regulate transcription inside the cell while outside the cell it serves as an alarmin to activate the innate immune system and promote tissue repair. The translocation of HMGB1 which takes place primarily during cell activation and cell death is vital to it immunological activity and may undergo PTMs similar to those determining the epigenome [8]. Modifications of HMGB1 influence its location in the cell as well as its immunological activity whereas epigenetic modifications usually influence gene expression.

The immunological activity of HMGB1 depends on exposure to cells of the innate immune sys-

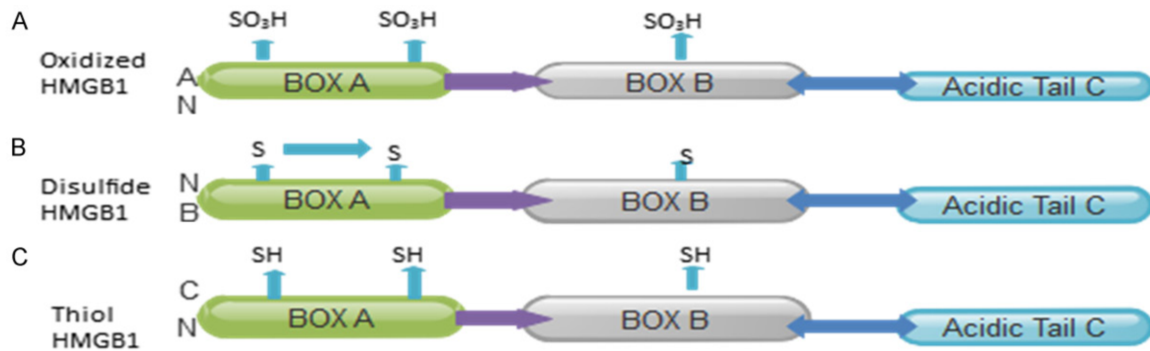

Figure 1. Different HMGB1 redox states: A: The oxidized isoform has all-oxidized cysteine in HMGB1and is seen as noninflammatory; B: The Disulfide isoform has a disulfide bond that induces cytokine cell release; C: The thiol isoform has a reduced cysteine with chemoattractant activity.

tem hence its translocation or release from cells usually occurs in the settings of activation and cell death. It's release during cell death makes it play a role as an alarmin. In vitro studies have demonstrated a variety of cell systems with several distinct mechanisms by which HMGB1 is released from cells that importantly may involve PTMs. These modifications can change the location of HMGB1 as well as its interaction with chromatin. It is well noted that over 100 different PTMs like methylation, phosphorylation, acetylation, ribosylation and ubiquitination characterize the epigenome [9, 10]. We will discuss in details the PTMs (acetylation, methylation and phosphorylation, oxidation, glycosylation and ADP-ribosylation) of the HMGB1, highlighting how these PTMs affect the functions of the HMGB1 in an array of cellular and extra cellular processes and also look at the role of HMGB1 in disease (e.g. cancer) and therapy.

The redox and oxide status of HMGB1

HMGB1 contains three cysteine residues. Two of these cysteine residues form a disulphide bond, and all three are sensitive to oxidation status in the environment. With recent sub-standard agreement, the three major isoforms of HMGB1 have been termed 'disulphide HMGB1', 'thiol HMGB1' and 'oxidized HMGB1' [11-14] **Figure 1**. These isoforms have pleiotropic activities like any other cytokine and the activities depend on the cellular compartment of action, the reciprocal receptor and the specific molecular structure of the isoform. The principal isoform released during necrosis is thiol HMGB1 while the disulphide HMGB1 isoform is the main isoform that accumulates in the extracellular space and serum compartment during acute and chronic inflammation. HMGB1 is a pro-inflammatory cytokine-like molecule that activates macrophages/monocytes and other cells to produce cytokines and additional inflammatory mediators. The oxidized HMGB1 isoform is seen as noninflammatory, although previously unsuspected roles of this molecule are yet to be elucidated. Researchers have established the HMGB1 release from ischemic cells is an early event in response to injury [3, 12, 15].

Function of HMGB1

HMGB1 is a unique, ubiquitous and highly expressed nuclear protein which stabilizes nucleosome formation and facilitates transcription factor binding to DNA. Outside the cell it may function as a potent cytokine with the ability to trigger inflammatory mediators [16]. In damaged or dying cells, passive release of HMGB1 is by cell necrosis and not apoptosis and it's a chemoattractant for immature dendritic cells (DCs) and promotes their maturation [4]. Studies have shown that HMGB1 lacks a signal sequence. Furthermore, monocytic cells receiving inflammatory signals can acetylate it's interfering with nuclear localization signals and allowing secretion [17]. Dumitriu *et al* indicated that DCs can secrete HMGB1, and such secretion promotes proliferation and Th1 polarization of interacting T cells [18]. Additionally, several studies have indicated that HMGB1 can directly or indirectly contribute Th17 expansion [19, 20]. When unregulated, HMGB1 can contribute to immune-related pathology. It is also

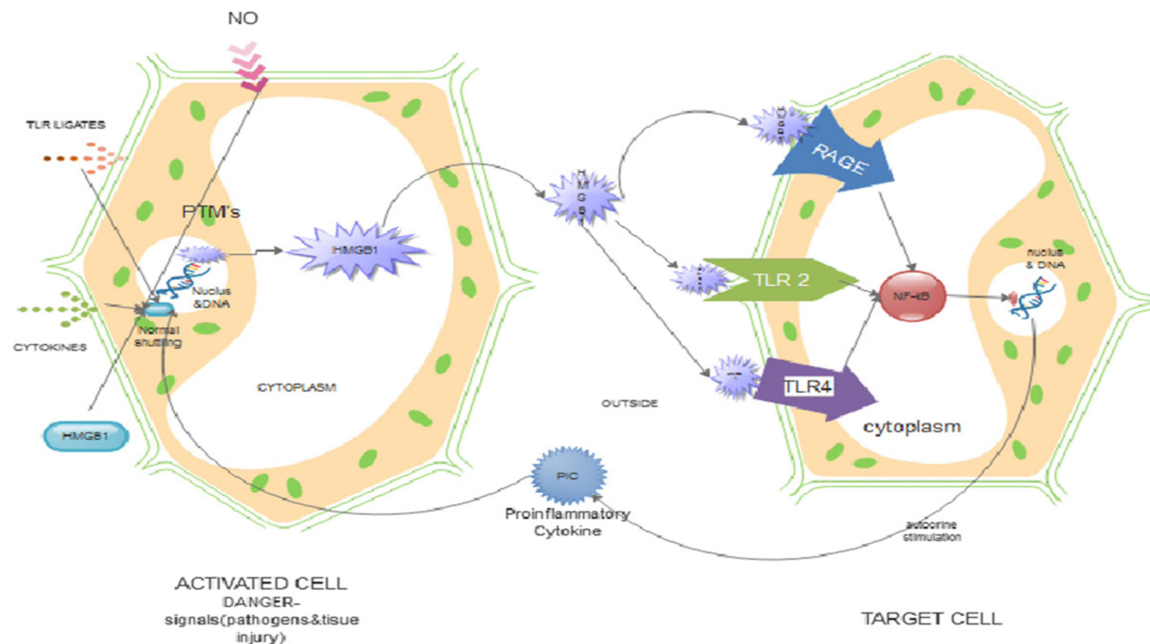

Figure 2. The role of post-translational modification (PTM) in translocation and immune activation by HMGB1. HMGB1 undergoes PTMs (e.g., acetylation, phosphorylation, methylation, etc.) following cell activation induced by external stimuli (necrotic cell or by active secretion from activated macrophages/monocytes). This modification leads to translocation of HMGB1 from the nucleus into the cytoplasm, into secretory endosomes and out of the cell. Extracellular HMGB1 functions as an immune activator by binding TLRs 2 and 4 and RAGE on immune cells like macrophages and neutrophils. Following binding, it leads to activation of gene expression via NF-kB. This explains the pro-inflammatory role HMGB1 during PTMs.

angiogenic and promotes cardiac stem cell growth and differentiation indicating its potential involvement in repairing damaged tissues [21]. It has direct and potent bactericidal activity just like defensins and cathelicidins [8]. Abeyama and colleagues have indicated that vascular thrombin binding protein, thrombomodulin (TM) is responsible for binding and sequestering HMGB1. It has protection effects which partially explains it's anti-inflammatory effects [22]. Researchers have shown that tissue damage caused by trauma, ischemia, hemorrhage or severe infection leading to sepsis may result in life-threatening out-of-control HMGB1 responses [23-25]. Inhibiting of HMGB1 has been effective in increasing survival in mouse or rat models of sepsis or hemorrhage [26] although 30% of patients do not survive due to organ failure and cardiac arrest even with intensive treatment for severe sepsis. Therefore, therapeutic strategies based on one or more of these inhibitors are attractive, especially considering fact that HMGB1 levels peak later than 24 hours after the initiation of sepsis, potentially allowing time for treatment to occur.

HMGB1 receptor and intracellular signaling

The mechanism by which HMGB1 interacts with target cells is still not well understood. RAGE is a transmembrane protein that is a member of the immunoglobulin (Ig) superfamily and is homologous to a neural cell-adhesion molecule [27]. It is expressed in central nervous system, endothelial cells, smooth muscle cells, and mononuclear phagocytes. It has been found that HMGB1 is a specific and saturable ligand for RAGE. It has higher affinity for RAGE than other known ligands such as advanced glycation end products (AGEs) [28]. Studies have shown that HMGB1-RAGE interaction will also lead to phosphorylation of MAP-kinases p38, p42/p44, and c-jun NH2-terminal kinase, resulting in NF-B activation [29, 30]. Furthermore, extracellular proteolytic activity induced by HMGB1 expressed on the leading edge of motile cells has also recently been confirmed in an experimental tumor system [29] (**Figure 3A**).

Researchers have also indicated that HMGB1 being a "sticky" molecule, binds to many mem-

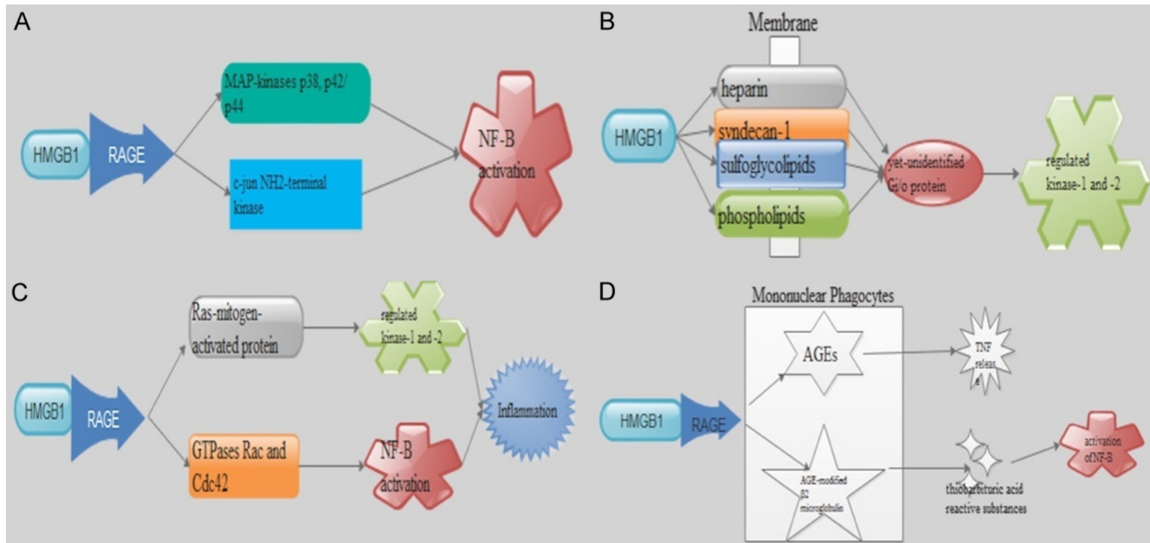

Figure 3. Potential HMGB1 receptor and possible signaling pathways. A: HMGB1-RAGE interaction leads to phosphorylation of MAP-kinases p38, p42/p44, and c-jun NH2-terminal kinase, resulting in NF-B activation. B: HMGB1 binds to many membrane molecules such as heparin, proteoglycans including syndecan-1, sulfoglycolipids, and phospholipid and mediate phosphorylated of extracellular regulated kinase-1 and -2. That involves signaling via an unidentified Gi/o protein. C: HMGB1 through RAGE can activate two different cascades, one involving the involves the Ras-mitogen-activated protein (MAP) kinase pathway and a second that involves a small GTPases Rac and Cdc42 leading to cytoskeletal reorganization and subsequent nuclear factor (NF)-B nuclear translocation-mediating inflammation. D: RAGE is also expressed on mononuclear phagocytes where its interaction with AGEs enhances cellular oxidant stress and generation of thiobarbituric acid reactive substances and activation of NF-B. RAGE signaling has also been shown to stimulates an inflammatory response when AGE-modified β2 microglobulin binds RAGE in mononuclear phagocytes to mediate monocyte chemotaxis and induce TNF release.

brane molecules such as heparin, proteoglycans including syndecan-1, sulfoglycolipids, and phospholipids [31, 32]. Also, HMGB1-mediated movement of smooth muscle cell involved in the activation of the MAP-kinase pathway. Additionally, nuclear translocation of phosphorylated extracellular regulated kinase-1 and -2. is involved in cell signaling via an unidentified Gi/o protein [30] (**Figure 3B**). Induction of intracellular signaling by HMGB1 through RAGE can activate two different cascades, one involving the involves the Ras-mitogen-activated protein (MAP) kinase pathway and a second that involves a small GTPases Rac and Cdc42 leading to cytoskeletal reorganization and subsequent nuclear factor (NF)-B nuclear translocation-mediating inflammation [33] (**Figure 3C**). RAGE is also expressed on mononuclear phagocytes. Also, its interaction with AGEs enhances cellular oxidant stress [34] and generation of thiobarbituric acid reactive substances and activation of NF-B [33] (**Figure 3D**). RAGE signaling has also been shown to stimulates an inflammatory response when AGE-modified β2 microglobulin binds RAGE in mononuclear phagocytes to mediate monocyte chemotaxis and induce TNF release [34]. However, it has been found that HMGB1-induced differentiation of erythroleukaemia cells is independent on RAGE signaling. This suggest that there may be additional signaling HMGB1 receptors yet to be identified [35]. Meanwhile Tumor growth and metastasis was suppressed when HMGB1 was prevented from interacting with RAGE using RAGE-blocking antibodies or neutralizing anti-HMGB1 antibodies. RAGE has been implicated in the pathogenesis of multiple diseases such as diabetes, atherosclerosis, and Alzheimer's disease [36, 37]. It is also indicated that cell membrane-associated HMGB1 signals neurite outgrowth by interaction with the multi-ligand receptor RAGE [28]. Potential dangerous signs may occur when local binding of HMGB1 restricts the diffusion of extracellular HMGB1 and inhibit systemic release.

Cellular sources of HMGB1

Current studies have shown that HMGB1 is normally located in the nucleus and translocates from the nucleus to the cytosol, including mitochondria and lysosome, following various

stressors (e.g., cytokine, chemokine, heat, hypoxia, H_2O_2, and oncogene). Although the function of cytosolic HMGB1 still remains poorly understood, there is evidence that the main function of HMGB1 in cytoplasm is to provide positive regulator of autophagy, which was first reported in 2010 [38]. It is also now clear that HMGB1 is expressed in the nucleus of all vertebrate cells. In contrast, only resting human platelets express cytoplasmic HMGB1, which is exported to the cell surface during platelet activation. On the other hand, activated mononuclear phagocytes and pituicytes have developed the ability to translocate their nuclear HMGB1 to the cytoplasm [39]. Whether there are additional cell lineages that enable resting human platelets to express cytoplasmic HMGB1 that is exported to the cell surface during platelet activation is still not well understood but it is well established that HMGB1 associates with plasminogen and tissue plasminogen activator on cell surfaces and enhances plasminogen generation and proteolysis [40, 41]. Understanding of signaling mechanism of cellular HMGB1 focus on the design of sepsis therapeutics that interferes with activation of blood clotting systems but it will be important to delineate the connection between neutralization of HMGB1 and coagulation mechanisms, as these two systems occupy a critical and finally a common pathway to tissue injury and death from sepsis.

Extracellular HMGB1 release

HMGB1 can be passively secreted from the nuclei of necrotic cells, damaged cells or actively secreted from activated macrophages/monocytes or pituicytes which does not involve cell death (**Figure 2**). These process ware not known until recently [7]. However, HMGB1 does not have a leader sequence and hence not processed via the endoplasmic reticulum/Golgi pathway. This is characterized by a few secreted proteins such as fibroblast growth factor and IL-1β. Pulse-chase labeling with 35S-methionine showed that extracellular HMGB1 was newly synthesized during the first 12 h after TNF stimulation with macrophages from a preformed pool [42]. Further studies have indicated that cultured, activated macrophages will translocate their nuclear HMGB1 to the cytoplasm before extracellular release via lysosomal exocytosis [7].

HMGB1 and post translational modifications

PTMs of HMGB1 protein have not been investigated as extensively as those of other HMG proteins but accumulating evidence has shown the remarkable biological significances induced by the post-translational: acetylation, methylation and phosphorylation, oxidation, glycosylation and ADP-ribosylation of the HMGB1 protein to modulate its interactions with DNA and other proteins.

Phosphorylation

Earlier studies indicate that HMGB1 isolated from lamb thymus could be phosphorylated by calcium/phospholipid-dependent protein kinase but not by cAMP-dependent protein kinase. Serine residues were phosphorylate in HMGB1 and a minimum of at least six phosphorylation sites were suggested [15]. Youn and colleagues found that HMGB1 can be phosphorylated in RAW264.7 cells and human monocytes after treatment with TNF-α or okadaic acid, a phosphatase inhibitor, resulting in the transport of HMGB1 to the cytoplasm for eventual secretion [15]. In their study, the phosphorylation sites were not identified but the possible phosphorylation sites were suggested to be Ser-34, Ser-38, Ser-41, Ser-45, Ser-52 and Ser-180, which reside mainly around NLS1 and NLS2 signal regions in the nucleus [15]. There is currently no study about the exact phosphorylation sites as well as the corresponding kinases involved in this process hence further studies will provide a better understanding of phosphorylation-controlled nuclear export of HMGB1.

Acetylation

Sterner *et al* in 1979 were the first to describe reversible acetylation of HMGB1 by incubating calf thymus homogenates with 3H-labeled acetate. Automated Edman degradation of the intact 3H-labeled HMGB1 revealed that two lysine residues in the N terminal region of the protein, Lys-2 and Lys-11, were acetylated [43]. HMGB1 acetylated/deacetylated by the same enzymes such as those acting on histone H4, indicated the roles of histone acetyltransferases (HATs) and histone deacetylases (HDACs) in the dynamic acetylation of HMGB1 protein [43].

It is also noted that the modification site was Lys-2 when the acetylated HMGB1 protein, iso-

lated from cells grown in the presence of sodium n-butyrate, exhibited significantly enhanced ability to recognize UV light- or cisplatin-damaged DNA and four-way junction [44]. HMGB1 is an *in-vitro* substrate for CBP, but not for PCAF or Tip60, and the full-length HMGB1 is monoacetylated at Lys-2. Furthermore, the removal of the C terminal acidic tail of HMGB1 resulted in increased acetylation, catalyzed by CBP, at Lys-2 and a novel target site at Lys-81 [45]. HMGB1 is located in the nucleus in most cells and recent studies has demonstrated that HMGB1 could be secreted by monocytes and macrophages [46]. It can also passively leak out of cells during necrosis [5]. HMGB1 lacks a secretory signal peptide and doesn't traverse the ER-Golgi system hence the secretion of this nuclear protein seems to require a tightly controlled relocation program [17]. It's also well noted that, in monocytes and macrophages, HMGB1 can be extensively acetylated in such a way that the protein can be relocated from the nucleus to cytoplasm and eventually secreted out of the cell [17]. In resting macrophages, HMB1 can be forced to translocate from the nucleus to the cytosol via hyperacetylation with the aid of different proteolytic enzymes such as trypsin, Glu-C, and Asp-N, alone or in combination. Trypsin, Glu-C, and Asp-N are usually employed for the digestion, and the resulting peptides analyzed by MALDI-MS. Totally 17 lysine residues were suggested to be acetylated, among which Lys-27, Lys-28, Lys-29, Lys-179, Lys-181, Lys-182, Lys-183 and Lys-184 were the major acetylated residues, and all of them were within the nuclear localization signal regions [17].

Methylation

Ito *et al* in 2007, demonstrated the mono-methylation of lysine in HMGB1 isolated from neutrophils, which regulated its relocalization from the nucleus to cytoplasm, with the methylation site mapped at Lys-42. The methylation led to conformational changes of HMGB1 proteins. They indicated that most methylated HMGB1 resides in the cytoplasm of neutrophil, whereas un-methylated HMGB1 exists in the nucleus. They further stated that the possible mechanism for methylation-controlled distribution was that methylation of Lys-42 altered the conformation of box-A, thereby weakening its ability to bind to DNA. Also, methylated HMGB1 is distributed in the cytoplasm through passive diffusion from the nucleus [47]. Although HMGB1 was found to be methylated only in neutrophils, they suspect that this is not unique because the cytoplasmic release of HMGB1 also exists in other cells, which could also be controlled by its PTMs such as methylation.

Oxidation

It's now clear that HMGB1 contains three cysteines, Cys23, 45, and 106 with Cys23 and 45 inducing conformational changes in response to oxidative stress, while Cys106 is critical for HMGB1 translocation from nucleus to cytoplasm. Also, reduction in inflammatory activities may be caused by the oxidation of Cys106 within the HMGB1 molecule [48]. Studies have shown that oxidation of Cys106 is necessary to block the stimulatory activity of HMGB1 [48]. Binding of HMGB1 to macrophages toll-like receptor 4 and Cys106 has also been reported [49]. Alterations such as the mutation of Cys106 also prevented the HMGB1-induced activation of cytokine release by cultured macrophages [49]. Injection of rHMGB1 to mice led to an acute inflammatory injuries in the lungs with neutrophil accumulation and development of lung edema as well as increased pulmonary production of inflammatory cytokines [50]. It's now well documented that oxidation of HMGB1 reduce inflammatory activity both *in-vitro* and *in-vivo*. Reactive oxygen species (ROS) is noted to significantly promote HMGB1 translocation and release in activated immune cells or injured cells [51] which means that ROS is a major signal that decreases nuclear HMGB1 DNA binding activation hence promotes cytoplasmic translocation and release. The redox status of HMGB1 in terms of location and release directly influences its extracellular activity, such as immunity and autophagy [52].

Glycosylation

HMGB1 N-glycosylation is a prerequisite critical for nucleocytoplasmic translocation and extracellular secretion. Young and colleagues indicated that HMGB1 can be N-glycosylated at Asn37 and alternatively at Asn134/135 residues. This determines the nucleocytoplasmic transport, extracellular secretion, and protein stability of HMGB1. They noted two N-glycosylations at Asn37 and Asn134, with the consensus motifs of Asn-Xxx-Ser/Thr, and at the non-classical consensus residue Asn135 using

recombinant HMGB1 proteins produced in both HEK293T and insect cells [53]. Recently, the sequence requirements of the acceptor substrate for N-glycosylation have become less strict; atypical (non-consensus) Asn-linked glycosylation is possible [54, 55]. N-glycans are synthesized and transferred to polypeptides containing a signal peptide via glycosyltransferase to Asn residues within the Asn-Xxx-Ser/Thr sequon in the luminal side of the ER and Golgi apparatus [56]. The interaction of the autophagy-based unconventional secretion of HMGB1 and its glycosylation is needed to further identify and understand the pathophysiologic mechanism of HMGB1-mediated inflammation.

ADP-ribosylation

The addition of one or more ADP-ribose moieties to a protein by ADP-ribosyl transferases is termed ADP-ribosylation. Hassa and colleagues in their study classified ADP-ribosylation reactions into four groups: mono-ADP-ribosylation, poly-ADP-ribosylation, ADP-ribose cyclization, and formation of O-acetyl-ADP-ribose [57]. Hyper ADP-ribosylation of HMGB1 downregulates gene transcription since ADP-ribosylation is generally inversely related to transcription. PARP1-mediated poly-ADP-ribosylation reactions are required for the nuclear export and release of HMGB1 during cell death, especially necrosis and not mono-ADPribosylation alone [58, 59]. Hyper poly (ADP-ribosylated) HMGB1 enhances inhibition of efferocytosis by binding to PS and RAGE when released [60] but lack of intracellular HMGB1 leads to excessive PARP1 activation and injury [61] hence cross linkage between HMGB1 and PARP1 in ADP-ribosylation reaction in regulating cell death.

Post translational modifications of HMGB and nuclear export

Bustin and colleagues proposed that there are two DNA-binding motifs on the HMGB1 protein, two nuclear localization signals and two putative nuclear export signals [62], There is enough evidence that the PTMs of HMGB1 also controlled the shuffle of this protein between the nucleus and cytoplasm through PTMs in the HMGB box-domains which regulates HMGB1's biological function in gene transcription, [7, 15, 17, 47]. Phosphorylation at both NLS sites is important in blocking HMGB1 re-entry to the nucleus and in the accumulation in the cytoplasm [15]. There is indication that the subcellular localizations of HMGB1 depends on its acetylation with deacetylase inhibitors causing the relocalization of HMGB1 from nucleus to the cytoplasm, and mutation of six major acetylation sites to glutamine, which mimics an acetylated lysine thereby inducing the relocalization of HMGB1 to the cytoplasm [17]. Nevertheless, methylation of HMGB1 in neutrophils could weaken its binding to DNA and causing its cytoplasmic relocalization in neutrophil through passive diffusion out of the nucleus [47]. The PTMs of HMGB1 and nuclear export clearly shown in **Figure 2**. It's still not clear as to which specific modification is dominant, although all the PTMs plays important but different roles in HMGB1's localization in cytoplasm under physiological conditions.

HMGB1 measurements and significance in clinical practice

Atkinson *et al* defined biomarkers as characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention [63]. Many researchers have tried to evaluate the level of HMGB1 in samples (e.g., serum, plasma, cerebrospinal fluid, sputum, urine, fecal, and tissue) as a biomarker of human disease which can be used for detection and diagnosis of disease as well as prediction of response to therapeutic interventions and prognosis of outcome. They found out that circulating HMGB1 levels have been positively or inversely associated with sRAGE levels pointing to a fact that sRAGE not only regulates HMGB1 activity but also eliminates circulating HMGB1 in human disease [64]. Although ELISA and Western blot are the two methods used to detect HMGB1 in serum, plasma, and body fluid, HMGB1 levels in serum or plasma maybe five times higher when analyzed by Western blot as compared to ELISA because serum and plasma components (e.g., immunoglobulins, phospholipids, thrombomodulin, and proteoglycans) can interfere with the detection of HMGB1 detection via ELISA [65].

Barnay-Verdier and colleagues indicated that perchloric acid modified ELISA can detect masked forms of HMGB1 [66] but now several new techniques (e.g., DNA nanostructure-based assay) have shown dominance in detecting HMGB1 concentration in serum or superna-

tants [67]. Nevertheless, immunohistochemical staining is widely used in the detection of HMGB1 expression and localization in tissues while RT-PCR and q-PCR are widely used to test HMGB1 mRNA expression in tissues. HMGB1 gene polymorphisms are involved systemic inflammatory response syndrome [68, 69] and several human disease and notable among this disease are chronic HBV infection [70], trauma [71], allogeneic hematopoietic cell transplantation [72]. Also Serum anti-HMGB1 autoantibody is increased in several autoimmune diseases [73].

The role of HMGB1 as a mediator of disease and target of therapy

Strategies such as antibodies, peptide, RNAi, anti-coagulant agents, endogenous hormones, chemicals including natural product, HMGB1-receptor and signaling pathway inhibition, artificial DNAs, physical methods (e.g., medical hydrogen gas), vagus nerve stimulation, and surgery have been proposed from cell, animal, and human studies to inhibit HMGB1 expression, release, and activity in a direct or indirect manner.

HMGB1 has multifunctional activities in the immune system and can induce a lot of host responses such as cell proliferation, cytokine production and increased expression of cell-surface molecules involved in inflammation. Whereas these activities resemble those of cytokines such as TNF-α and IL-1, there is enough evidence that this protein mediates disease is extensive and derives from two main sources: (1) demonstration that blockade of HMGB1 ameliorates disease in animal models and (2) demonstration of extracellular HMGB1 or cellular translocated HMGB1 in tissue or the blood from either animal models or patients with disease. Studies have now shown that HMGB1 is not only expressed in sepsis but also in wide range of disease such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome and stroke among many others [25, 74-79]. As various researches are still on going on HMGB1, the list will undoubtedly grow and it is likely that HMGB1 contributes to the pathogenesis of diseases in which immune-cell activation or cell death occurs.

Systemic lupus erythematosus is one of the diseases where HMGB1 may promote pathogenesis characterized by abnormalities in the extent of apoptotic death as well as impairment in the clearance of apoptotic cells. During the pathological process of the disease, inflammation which is usually a cardinal sign is incites when immune complexes comprised of nuclear macromolecules and anti-nuclear antibodies form and deposit in the tissue and these complexes usually stimulate the production of interferon α/β by plasmacytoid dendritic cells, a response that depends upon TLR9 as well as the Fcg receptor IIα [80, 81]. The response above may involve HMGB1, which serves as a component of these complexes and stimulates responses via RAGE and also promote responses to DNA in complexes via its interaction with TLR9 [82].

In diseases where HMGB1 may be pathogenic, mechanisms to block the effects of HMGB1 focus on the antibodies or other agents that bind to it and therefore prevent its interaction with its receptors [23, 26, 83-85] and both TLR2 and TLR4 can serve as receptors for HMGB1 while RAGE appears to play a major role in the response to this protein [82, 86, 87]. While antibodies to RAGE have been used widely to treat inflammation in animal models with their efficacy potentially including blocking of HMGB1-receptor interactions, the isolated domain of HMGB1 can block the effect of the intact protein and A-box construct can attenuate disease in animal models of collagen-induced arthritis [88].

Most therapies target HMGB1 after it has left the cell but it important to note that strategies to target the release of HMGB1 is also possible. These mechanisms involve inhibitors of PTMs although their effects maybe broader if the same enzymes modifying HMGB1 also modify histones. Initial studies have demonstrated that gold salts a group of compounds that were initially the standard treatment of rheumatoid arthritis can block the release of HMGB1 from murine macrophages stimulated by LPS *in-vitro* by gold thiomalate. This effect was specific because gold thiomalate did not affect the release of TNF-α from these cells [89]. Although gold has other immune effects, it is possible that its anti-rheumatic activities is as a result of mechanisms that involved modification or translocation of HMGB1 during activation or a subsequent step in the intracellular trafficking.

Ostberg and colleagues have also demonstrated that Platinum compounds can also block HMGB1 release from macrophages. Therefore, they are very effective in animal models of arthritis [90]. They explained that these compounds can chemically modify DNA and create DNA adducts that avidly bind HMGB1. Although the mechanisms of action of gold and platinum still needs further investigation, these initial studies suggest a potential new target for the therapy of inflammatory and autoimmune disease.

HMGB1 and cancer

Many researchers have implicated the major role HMGB1 players in a number of cancers including colon, breast, lung, prostate, cervical, skin, kidney, stomach, pancreatic, liver, bone, and blood cancers [91-95]. Depending on the context, the study conditions, the location and modification, HMGB1 acts as both a tumor suppressor and an oncogenic factor in tumorigenesis and cancer therapy [96]. Sustainment of proliferative signaling; evasion of growth suppressors; avoidance of immune destruction; enablement of replicative immortality; tumor-promoting inflammation; activation of invasion and metastasis; induction of angiogenesis; genome instability and mutation; resistance to cell death; and deregulation of cellular energetics where the ten fundamental properties that drive tumor development and growth as proposed as Cancer hallmark by Hanahan and Weinberg in their cancer update [2, 97].

Oncogenic roles in tumorigenesis

Studies have shown that the tumor microenvironment is usually made up of tumor cells, non-tumor cells and several immune cells and HMGB1 is released together with autocrine from the tumor cells and the surrounding cells under hypoxia or other environmental stimuli [98-101]. It's well noted that extracellular HMGB1 mediates communication between cells in the tumor microenvironment by several receptors (e.g., RAGE and TLR4). These receptors contributes to tumor growth and spreads by several mechanisms including sustenance of the inflammatory microenvironment [102-104], fulfillment of metabolic requirements [96, 105], promotion of invasion and metastasis [106] inhibition of antitumor immunity [107], and promotion of angiogenesis [100, 108], hence inhibition of HMGB1 release and activity can block tumor growth and development.

Tumor suppressor roles in tumorigenesis

Jiao and colleagues have indicated that HMGB1 binds to tumor suppressor RB, which leads to RB-dependent G1 arrest and apoptosis induction and prevents tumorigenesis in breast cancer cells *in vitro* and *in vivo* [109] which support early finding that intracellular HMGB1 maybe a tumor suppressor. Studies have shown that nuclear HMGB1 is an important architectural factor with DNA chaperone activity therefore loss of HMGB1 leads to genome instability with telomere shortening, which is major driving force in tumorigenesis [110] and that deficiencies of autophagy gene (e.g., Beclin-1, ATG5, UVRAG, Bif-1) increase tumorigenesis due to genome instability, inflammation, and organelle injury [111]. HMGB1 deficiency leads to autophagy dysfunction and may cause genome instability and inflammation which promotes tumorigenesis since HMGB1 is a positive regulator of autophagy [38, 105]. The translational potential of the above findings is still not clear hence further research is needed to come with concrete explanations.

Sensitivity to anticancer therapy

Cancer cell death can be immunogenic or non-immunogenic depending on the type of anticancer therapy [2, 112, 113]. HMGB1 when released by dead or dying cells can mediate immunogenic cell death and subsequent anti-tumor immunity and tumor clearance by binding to TLR4 [13, 114-116]. It is now clear that TLR2, but not TLR4 in DCs, mediates the T-cell-dependent antitumor immune response that induces brain tumor regression [13, 117] which suggest that HMGB1 release contributes to anticancer immunity. On the other hand, HMGB1 released during cell death may mediate immunogenic tolerance if it binds to TIM-3 or undergoes a redox transformation to oxidized form [118]. Luo *et al* demonstrated that remnant cancer cells has the ability to regrow and metastasize in a RAGE-dependent way when HMGB1 is released during chemotherapy [119] therefore the inhibition of HMGB1-RAGE pathway improves the effectiveness of chemotherapy [120]. It's now clear that the activity of HMGB1 in anticancer immune response depends on many factors including receptor, death type, and redox state.

Resistance to anticancer therapy

Studies have shown that intracellular HMGB1 is generally negative regular for the effectiveness of anticancer therapy while extracellular HMGB1 play a significant role in anticancer therapy. Many chemotherapy agents including platinating agents have proven by researchers to increase HMGB1 expression [2, 121] hence HMGB1 is becoming a recognized therapeutic target for chemotherapy resistance. It's well known that RNAi down regulates HMGB1 expression and increased the anticancer activity of cytotoxic agents, while gene transfection up regulates HMGB1 expression and increase drug resistance [122, 123]. It's clear that increased HMGB1 expression in cancer cells facilitates chemotherapy resistance partly through inhibition of apoptosis and promotion of autophagy, which determine cell fate in anticancer therapy [120, 122-125] but differs in the regulation of chemotherapeutic agent toxicity in cancer cells and normal cells [126]. The actual processes by which these differences occur need further investigation.

Conclusion

Our review points out clearly that HMGB1 protein is essential in chromatin dynamics and influences various DNA processes in the context of chromatin, which include PTMs. Up or down regulation of HMGB1 levels modifies the cellular phenotype and lead to developmental abnormalities and diseases. Therefore, characterization of these chemical modifications of HMGB1 protein will provide significant insights into the mechanism of action of this protein which may eventually lead to improved detection, therapy and prognosis of human diseases. It's now also clear that HMGB1 can be inhibited by administration of specific and nonspecific binding proteins, including antibodies, HMGB1 A box, sRAGE, thrombomodulin and haptoglobin and can be a potential for target in sterile inflammation and injury. The development of future therapeutic agents targeting intracellular HMGB1 biology will require further understanding in the following directions: (i) the role of HMGB1 in autophagy, (ii) sensing of intracellular foreign nucleic acids and (iii) nucleosome formation. While we have outlined the role of PTMs of HMGB1 and several disease conditions such as inflammations, autoimmune diseases and cancer further studies is still needed to gain more insight into these modifications of HMGB1 and specific diseases entities.

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Disclosure of conflict of interest

None.

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