Review

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Sterile Inflammatory Role of High Mobility Group Box 1 Protein: Biological Functions and Involvement in Disease

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Abstract
High mobility group box 1 protein (HMGB1), a sterile inflammatory molecule and damage-associated molecular pattern (DAMP) released from various cells during stress has been implicated in inflammation. Several reports show that there is a direct relationship between inflammation and cardiovascular diseases (CVDs) such as thrombosis, hypertension, insulin resistance, preeclampsia, etc. Here, we intend to summarize the concept of the emerging link between HMGB1 and CVDs. Furthermore, we will discuss the possible therapeutic strategies that target HMGB1 for the treatment of different CVDs.

What Are Damage-Associated Molecular Patterns?

Damage-associated molecular patterns (DAMPs) are endogenous intracellular molecules released in the early phases of nonprogrammed cell death to signal danger cues in the early phase of cell injury. These molecules are also called alarmins [1]. Alarmins, include molecules such as high mobility group box 1 protein (HMGB1), adenosine triphosphate (ATP), uric acid, interleukin (IL)-1α, and circulating or cell-free DNA and RNA.

What Is HMGB1?

HMGB1 is a low-molecular-weight, highly conserved, nonhistone protein (25 kDa) with cytokine-like activity in the extracellular space. It consists of the DNA-binding domains, HMG A-box and HMG B-box in the N-terminus and a continuous stretch of aspartic and glutamic acid-rich negative charge in the C-terminal, respectively. HMGB1 is abundantly and ubiquitously expressed in the nucleus, where it plays a role in DNA replication, transcription, repair, and nucleosome stabilization [2]. It is also found in the cytosol and mitochondria and on the membrane surface, and it can be released to the extracellular milieu via active or passive pathways [3].

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The active secretory pathway in immune and nonimmune cells is switched on by the presence of pathogenic products (e.g., bacteria or viruses) or other cell stressors (i.e., cytokines and oxidative stress molecules) [4]. This is a slow pathway because it is mediated through cellular signal transduction [5]. On the other hand, the passive release pathway is fast-acting and occurs in tissue injury and cell death, especially in necrosis and sterile injury events including hypoxia, senescence, and autoimmune disease [6]. After release, HMGB1 accumulates in the extracellular milieu; thereafter, it relays danger signals in the local tissues by triggering inflammatory pathways such as nuclear factor (NF)-κB, extracellular regulated kinase (ERK), p38, CD24, Toll-like receptor (TLR)-2, TLR-4, and TLR-9, the receptor for advanced glycation end-products (RAGE), and others [2]. This results in the activation of innate and adaptive immunity, cytokine, chemokine, and metalloprotease release, and promigration and proinflammatory outcomes [3, 5].

HMGB1 has been shown to form complexes with multiple proinflammatory mediators, and thereby enhance their actions in a synergistic manner [7]. Animal models of different disease as well as human studies demonstrate elevated levels of HMGB1 [8]. In vivo experiments also showed HMGB1-induced inflammation while pharmacological intervention on the same molecular target ameliorated sepsis [9]. Over all, these studies suggest that HMGB1 plays a crucial role as a sterile inflammatory mediator for the development of diseases. The different important functions of HMGB1 are presented in detail.

The Role of HMGB1 as a Redox Regulator

Antoine et al. [10] classified HMGB1 into 3 subtypes according to the amino acid number of cysteine residues in the polypeptide chain: (a) fully reduced or all-thiol HMGB1 (HMGB1C23hC45hC106h), with no disulfide (S-S) bond among the cysteine residues as well as post-transcriptional modification (Fig. 1b); (b) disulfide HMGB1 (HMGb1C23-C45c106h), with an S-S bond between C23 and C45 (Fig. 1c); and (c) sulfonyl HMGB1 (HMGB1C23soC45soC106so) where the sulfate group is oxidized to form sulfonyl by reactive oxygen species (ROS) (Fig. 1d).

Fully reduced HMGB1 may promote leukocyte recruitment by binding to CXCL12 and CXCR4, suggesting that the reduced forms of the 3 cysteine residues contribute to its chemotactic activity [11, 12]. Platelet-derived HMGB1 has been shown to promote the recruitment of monocytes, and lead to inflammation and thrombosis [13]. Disulfide (or isomerized) HMGB1, characterized by 2 cysteine residues that are oxidized to form an S-S bond between C23 and C45, was found to induce NF-κB translocation and the secretion of inflammatory factors via TLR-4 in activated immune cells, while mutations of C23 or C45 abrogated the cytokine activity of HMGB1 [14]. It also induced bladder pain via TLR-4 [15]. Frank et al. [16] found that it potentiated the neuroinflammatory response in vivo, but that thiol HMGB1 failed to promote the microglial proinflammatory response to lipopolysaccharide (LPS). In line with this observation, a recent study showed that oxidative stress promoted the secretion of HMGB1 and other proinflammatory molecules, where HMGB1 was partially oxidized [17, 18]. However, in a vein thrombosis model, disulfide HMGB1, released from platelets and neutrophils, influenced neutrophil recruitment and the formation of neutrophil extracellular traps (NETs) that led to thrombosis via TLRs [19]. This suggests that HMGB1 isomerization might contribute to thrombosis through inflammation. The third form of HMGB1 is the sulfonyl or oxidized form which is characterized by 3 fully oxidized cysteine residues. In contrast to fully reduced/all-thiol HMGB1 and disulfide HMGB1, it has currently no known biological function such as chemokine and proinflammatory activities [20].

HMGB1 Signaling for the Initiation of Different Diseases

HMGB1 fundamentally resides in the nucleus under normal circumstances, stabilizing nucleosomes and facilitating gene transcription [21]. However, under different conditions, it becomes hyperacetylated, translocated from the nucleus to the cytosol, and then secreted actively or passively [22]. It has been shown that HMGB1 passively diffuses from various cells to the extracellular space during cellular necrosis or damage [6]. It is also actively released by macrophages, monocytes, and dendritic cells upon activation [23]. After release from these cells, it exerts its biological functions by interaction with RAGE [24, 25], TLR-2 [26], TLR-4 [27], and TLR-9 [28]. The consequences of these receptor-ligand interactions have been shown to induce cell adhesion [29], permeability [30], chemotaxis [31], inflammation [5], autophagy [32], thrombosis [19], and epithelial-mesenchymal transition [33]. In fact, the exact detailed mechanisms involved in disease progression are still not clear. The mechanism involving myeloid differentiation factor 88 (MyD88)-medi-

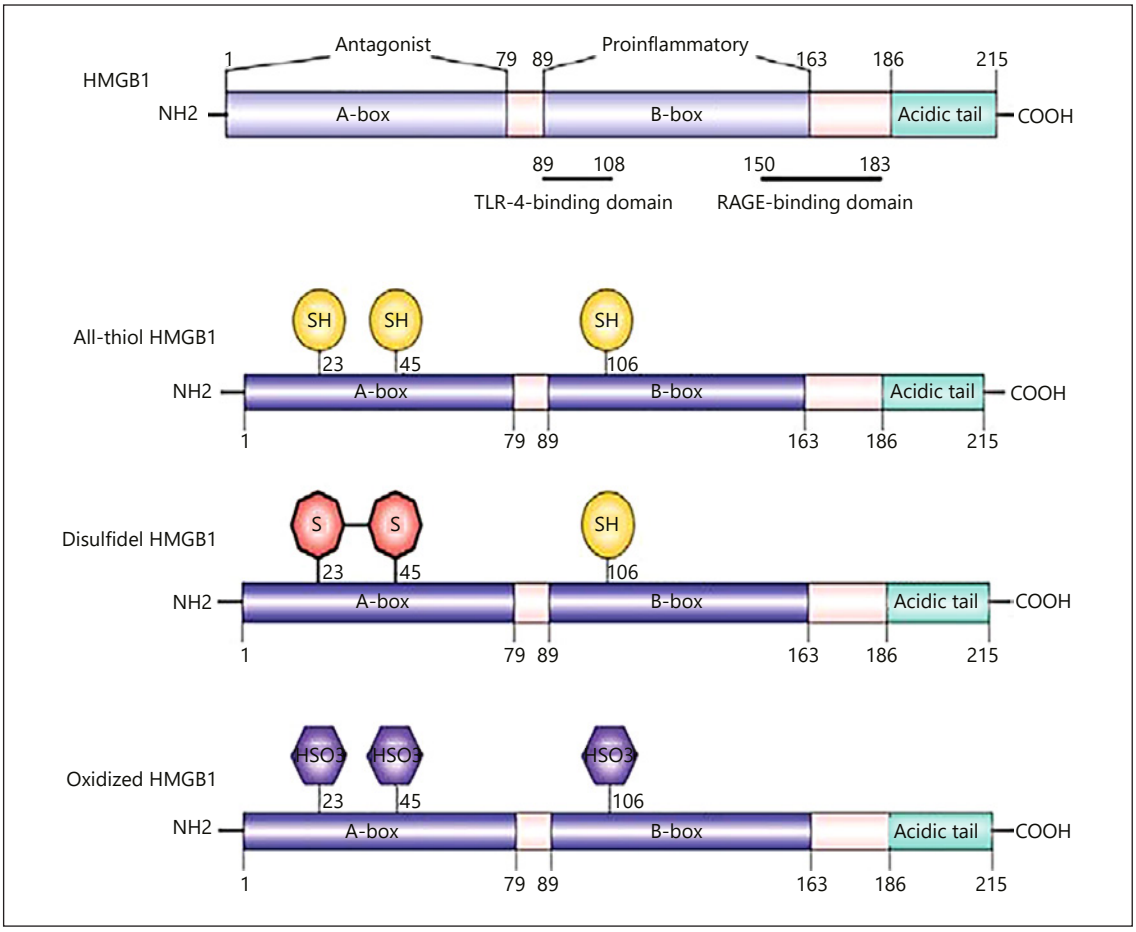

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Fig. 1. Structure and redox states of HMGB1. **a** HMGB1 consists of the A-box (anti-inflammatory domain), B-box (proinflammatory domain), and the acidic tail. Residues 89–108 were responsible for binding to TLR-4, whereas residues150–183 were responsible for binding RAGE. **b** All-thiol HMGB1 exhibited all reduced cystine residues at C23, C45, and C106. **c** Disulfide HMGB1 was formed by an S-S bond between C23 and C45. **d** Oxidized HMGB1 is characterized by all 3 oxidized cysteine residues at C23, C45, and C106.

ated pathways have been studied the most. One study showed that the mechanism of HMGB1-induced inflammation is mainly mediated via the MyD88-dependent pathway [34]. MyD88 knockout mice failed to release TNF-α in macrophages as well as IL-6 in a cold ischemic-reperfusion injury model [35, 36]. HMGB1 promoted antineutrophil cytoplasmic antibody-antigen translocation in neutrophils, which was abrogated by blocking TLR-4, RAGE, MyD88, and NF-κB [37]. Liu-Bryan and Terkeltaub [38] showed that a deficiency of TLR-2 and TLR-4 together, or MyD88 alone, diminished the HMGB1-induced expression of MMP-3 and MMP-13 in chondrocytes. Another study demonstrated that HMGB1 treatment increases the levels of proinflammatory markers in the lungs of wild-type mice but not in TLR-4–/– mice. An in vitro study demonstrated that pharmacological inhibition of TLR-4 or MyD88 also inhibited HMGB1-induced proinflammatory cytokine production [39]. Furthermore, it has been demonstrated that HMGB1 induces proinflammatory cytokine production in vivo via the TLR-4-MyD88-NF-κB pathway [40] (Fig. 2).

HMGB1 and CVDs

The Role of HMGB1 in Coronary Artery Disease

It is a well-established fact that HMGB1 has a very important role in the development of CVDs. In this regard, the first line of evidence showed that patients with coronary artery disease (CAD) had significantly higher plasma

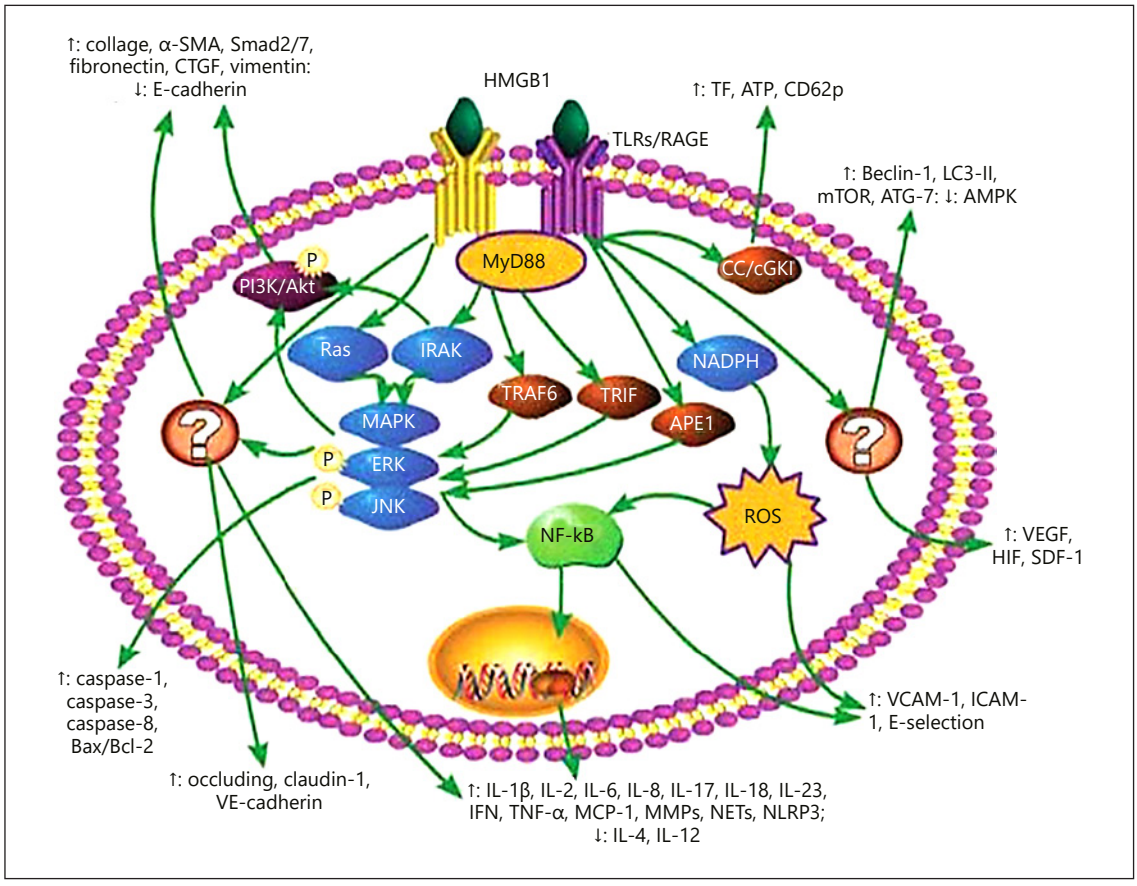

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Fig. 2. Signaling pathways of HMGB1. The interaction between HMGB1 and its receptors induced the activation of downstream signaling pathways during cell adhesion, permeability, chemotaxis, inflammation, immunization, autophagy, apoptosis, thrombosis, angiogenesis, fibrosis, and epithelial-mesenchymal transition.

HMGB1 when compared to control subjects [41, 42]. Another study showed that HMGB1 was significantly upregulated in the case of thrombosis (with plaque rupture) when compared with nonthrombotic subjects [43]. However, immunofluorescence data has demonstrated that HMGB1 is abundantly expressed in platelet-rich human coronary artery thrombi [44]. Furthermore, the plasma HMGB1 level in CAD is significantly higher in patients with plaque and chest pain when compared to normal subjects [43]. This suggests that HMGB1 plays a role in the development of atherosclerosis and CAD [45, 46]. Furthermore, ApoE–/– mice exhibited increased expression of HMGB1 in the aortic sinus [25]. Jin et al. [47] showed that the HMGB1 level is higher in patients with myocardial injury and after percutaneous coronary intervention. Therefore, HMGB1 has been considered a potential and independent predictor of cardiovascular mortality in patients with acute coronary syndrome and CAD [48].

The Role of HMGB1 in Stroke

A number of studies have suggested the relationship between HMGB1 and ischemic stroke. Several showed that the plasma HMGB1 level was elevated following ischemic stroke and correlated with the degree of sensitivity [49, 50]. Elevated HMGB1 is also associated with a poor outcome after ischemic stroke [51]. An animal study (stroke model) delineated that a higher level of HMGB1 is present in the serum [52], plasma [53, 54], and brain tissue of animals with stroke [55, 56]. Patients with peripheral arterial disease (PAD) had a higher plasma level of HMGB1 when compared to a control group [57]. A higher serum level of HMGB1 was observed in patients with type 2 diabetes mellitus, and this was exaggerated when PAD was also present [58]. HMGB1 level also increases in diabetic foot atherogenesis and influences its clinical outcome [59].

The Role of HMGB1 in Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a clinical syndrome characterized by the activation of the coagulation system. Increasing evidence supports the role of HMGB1 in DIC [60, 61]. Serum HMGB1 level was higher in patients with DIC when compared to controls [61]. It is therefore one of the predictive markers for the diagnosis of DIC. Moreover, higher HMGB1 in hematological malignancies might be complicated by the presence of DIC [62]. HMGB1 was also correlated with platelet activation markers in patients with DIC accompanied by hematologic malignancy [63]. However, patients with organ failure and nonsurvivors exhibit the highest HMGB1 levels among patients with DIC [61]. This suggests that elevated HMGB1 is directly associated with organ failure in DIC [60, 61].

The Role of HMGB1 in Deep Vein Thrombosis

Several studies have been reported on the role of HMGB1 in deep vein thrombosis (DVT). The expression of HMGB1 in brain tissue was higher in a cerebral vein sinus thrombosis when compared to the control group [64]. Furthermore, platelet-derived disulfide HMGB1 contributes to vein thrombosis as a central mediator of the sterile inflammatory process [19]. Numerous experimental and clinical studies have shown the role of HMGB1 in thrombosis-related diseases. However, the underlying molecular mechanism is still not clearly understood. We aim to discuss the mechanisms of DVT from 3 aspects: (i) platelet activation; (ii) NET formation; and (iii) fibrinolysis.

Platelets, enucleated cells in the blood, are believed to be centrally involved in thrombus formation. Upon activation, they release several molecules including serotonin, adenosine diphosphate (ADP), von Willebrand factor (vWF), thrombin, and certain growth factors from stored granules. This subsequently promotes platelet activation and aggregation via a positive-feedback mechanism, leading to thrombus formation and thrombosis.

Recently, it has been shown that inflammation also induces thrombosis. HMGB1 has been shown to play an important role in platelet activation and thrombosis [65]. After platelet activation, HMGB1 is translocated from the cytoplasm and onto the membrane surface where it exerts its effects [66]. HMGB1-treated mice also exhibit higher platelet concentrations than controls [67]. The mechanism of action could involve binding on the platelet membrane, which leads to further granular secretion and aggregation [68].

In another study, it was shown that a genetic deficiency of HMGB1(–/–) could increase bleeding time and induce platelet aggregation and thrombus formation [69]. Zhang et al. [70] demonstrated that LPS-activated platelet aggregation was mediated through the TLR-4 pathway. However, deletion of the *TLR4* gene resulted in decreased expression of P-selectin in platelets and caused the failure of aggregation in the presence of thrombin [71]. Yang et al. [68] showed that HMGB1/TLR-4-mediated signaling contributes to platelet activation and thrombosis. Another study demonstrated that platelets with genetically deleted HMGB1 (–/–) failed to aggregate [69]. Furthermore, ERK and guanylate cyclase (GC)/cyclic guanosine monophosphate (cGMP)/cGMP-dependent protein kinase I (cGKI) were found to be the downstream signaling pathways of TLR-4 in HMGB1-induced platelet activation and thrombosis [69].

NF-κB is the master transcriptional regulator for many genes. HMGB1 signaling has been shown to be mediated via the NF-κB pathway whereas inhibition of NF-κB impairs HMGB1-induced platelet activation and aggregation [68]. This finding suggests that NF-κB/IκBα is involved in HMGB1-induced platelet activation [68, 72]. Hence, HMGB1-induced platelet activation and aggregation are mediated via the TLR-4/NF-κB/IκBα/cGMP pathway.

The Role of HMGB1 in the Formation of NETs and the Development of Thrombosis

Sterile inflammation (SI) is non-pathogen-induced inflammation where stress or environmental factors play a major role. This type of inflammation has been implicated to be the pathophysiological basis of several CVDs like atherosclerosis, thrombosis, myocardial injury, insulin resistance (IR), and many acute conditions [26]. The relationship between HMGB1 and SI was reviewed in 2014 and studies have delineated the involvement of HMGB1 in the SI process [73]. Pharmacological inhibition of HMGB1 abrogates monocyte recruitment, leukocyte activation, and prothrombotic activity [19], suggesting that HMGB1, as an SI molecule, plays an important role in the development of thrombosis.

Neutrophil activation associated with the production of antibacterial peptides, reactive oxygen intermediates, cytokines, and other inflammatory mediators, as well as the release of DNA into the extracellular milieu, plays a central role in innate host defense and the modulation of inflammation [74]. NETs are produced through the release of DNA by neutrophils [74]. They are also formed in response to proinflammatory stimuli, including LPS, IL-8, and TNF-α, as well as through enhanced generation

of ROS by NADPH oxidase [74]. Tadie et al. [75] demonstrated that exposure of neutrophils to HMGB1 resulted in NETosis in vitro. They also showed that HMGB1-induced NETosis is mediated by TLR-4, which is consistent with previous studies that demonstrated that TLR-4 engagement enhances extracellular DNA release and the generation of NETs [75]. The TLR-4-MyD88 signaling pathway is mainly involved in NETosis through the release of DNA [76]. However, recent studies have shown that other signaling events, including the activation of NADPH oxidase or the stimulation of TLR-2, can also promote NETosis [77].

NETs contribute to venous thrombosis [78], DIC [79], and coronary thrombosis [80, 81]. NETs may also provide a milieu for vWF to facilitate the adhesion of platelets through surface receptors and lead to platelet activation [82]. The extracellular histones also facilitate platelet activation via the TLR-2 and TLR-4 pathways [83].

NETs stimulate both the extrinsic and intrinsic coagulation pathway [84]. Neutrophil elastase is known to cleave tissue-factor pathway inhibitor (TFPI) and enhance Factor Xa activity [85]. NETs contain neutrophil elastase which binds to TFPI and thereby facilitates the proteolytic inactivation of TFPI [86]. NETs also bind to Factor XII and stimulate fibrin formation via the intrinsic coagulation pathway [84].

Reduced NADPH is essential for biosynthetic reactions and antioxidant function through the generation of ROS [87]. ROS released by the NADPH oxidase complex can activate granular proteases and induce NETosis [88]. NADPH is also involved in HMGB1-induced activation of neutrophils [89, 90]. HMGB1 exert its effects on NETosis through TLR-2, TLR-4, and RAGE, which are dependent on NADPH oxidase [89]. Furthermore, TLR-4-dependent activation of NADPH oxidase is mediated via the MyD88-IL-1 receptor-associated kinase (IRAK)-(p38 mitogen activated protein kinase (p38 MAPK)/Akt signaling pathway [91].

HMGB1, Coagulation, and Fibrinolysis

Tissue factor (TF), also known as coagulation factor III, has been found to be involved in inflammation-related thrombosis [92]. HMGB1 can upregulate the expression of TF in monocytes [93]. HMGB1 also induces the expression and activation of TF in endothelial cells in a concentration- and time-dependent manner [93]. Its effect on TF activity induced by HMGB1 is partly attenuated by 3 neutralizing antibodies (anti-TLR-2, anti-TLR-4, and anti-RAGE) and NF-κB/early growth response-1 (Egr-1) interference, suggesting that the TLR-2/TLR-4/RAGE and NF-κB/Egr-1 pathway mediates the HMGB1-induced expression of TF [93]. HMGB1 also induces the formation of the plasminogen activator inhibitor-1/tissue plasminogen activator (PAI-1/tPA) complexes, suggesting that it might prevent fibrinolysis via increased PAI-tPA complexes in endothelial cells [94]. Collectively, these data provide evidence that coagulation and fibrinolysis factors are involved in HMGB1-induced thrombosis.

Nitric oxide (NO), a second-messenger molecule has been shown to inhibit platelet aggregation and thrombosis [95, 96]. During stress, HMGB1 is upregulated, which subsequently inhibits insulin-induced NO production [26]. In respiratory diseases such as chronic pulmonary disease (CPD) or obstructive sleep apnea (OSA), or in hypoxia, HMGB1 and vWF are unregulated and lead to the inhibition of NO production via the TLR-2-SP1-vWF pathway [97, 98]. HMGB1, as an endogenous ligand is released in the plasma due to hypoxic stress and thus inhibits NO production via the upregulation of vWF. HMGB1 also downregulates endothelial NO synthase activity in coronary endothelial cells through endothelial dysfunction [99].

The Role of HMGB1 in Hypertension

Recently, several studies showed that HMGB1 also plays a role in hypertension. Dange et al. [100] showed that hypertensive rats were found to have significantly increased levels of HMGB1 in the paraventricular nucleus of the hypothalamus as well as in the circulation. TLR-4 plays a role in hypertension, possibly via HMGB1. They also showed that the pathogenesis of hypertension is increased by the binding of HMGB1 to its specific receptors [100]. Nakamura et al. [101] showed a direct correlation of soluble RAGE and RAGE ligands like circulating HMGB1 in hypertensive patients, and recently, another study showed a direct relationship between HMGB1 and pulmonary hypertension [102].

The Role of HMGB1 in Preeclampsia

Preeclampsia (PE) is mainly developed due to reduced uteroplacental blood flow which causes the development of placental ischemia with oxidative stress, inflammation, necrosis, and structural damage [103]. Hypoxia and reduced nutrient supply are linked to exaggerated trophoblast cell necrosis [104]. These trophoblastic cells are rich sources of numerous alarmins such as uric acid, cell-free fetal DNA, HMGB1, and IL-1α; when they die, they release these alarmins into the extracellular environment which can result in a sterile inflammatory response [105].

HMGB1 is expressed by trophoblasts and can be found in either in their nucleus or cytoplasm [106]. Circulating levels of HMGB1 are increased in many inflammation-related diseases including PE [5]. Placentae exposed to aPL or PE sera are increased in the amount of cytoplasmic HMGB1 in the syncytiotrophoblast [5].

Pradervand et al. [107] showed that circulating levels of HMGB1 are higher in third-trimester PE than in normal pregnancies. This evidence suggests that HMGB1 plays a role in the development of PE.

HMGB1, an Innate Alarmin, and Its Role in the Pathogenesis of IR

It was recently rediscovered that HMGB1, an evolutionarily conserved chromosomal protein, acts as a "danger signal" (alarmin) to alert the innate immune system to trigger the host defense and/or tissue repair [32]. HMGB1 was initially found to be a DNA-binding protein that is present in almost all eukaryotic cells, where it stabilizes nucleosome formation and acts as a nuclear factor that enhances transcription [108]. Recently, HMGB1 secretion has been demonstrated in response to tissue damage, thus indicating a prototype of emerging DAMPs [21]. HMGB1 is also secreted by activated immune cells, including macrophages, dendritic cells, and natural killer cells in response to infection and inflammatory stimuli. It is now increasingly evident that HMGB1 plays a major role in several disease conditions such as atherosclerosis, diabetes, arthritis, sepsis, and cancer [109]. Once secreted, HMGB1 induces an inflammatory response by the transduction of cellular signals via its receptors, such as TLR-2, TLR-4, and RAGE. HMGB1 has been demonstrated to exert intracellular and extracellular functions by activating key oncogenic signaling pathways. Furthermore, HMGB1 also acquires or augments a proinflammatory effect via proinflammatory mediators such as LPS, IL-1, and DNA [110]. These observations indicate that HMGB1 is an essential mediator of organ damage; however, its precise role and mechanisms remain unknown. Studies have shown that high serum levels of HMGB1 contribute to the development of many inflammatory diseases and also diabetes [111]. Singh et al. [26] showed a direct relationship of the stress-induced upregulation of HMGB1 with IR, which is mediated through TLR-2. They further showed that stress-induced HMGB1 inhibited insulin-induced NO production through the upregulation of vWF [26, 98]. HMGB1 can signal through RAGE and TLRs to the NF-κB signaling pathway, and thus contributes to the inflammatory responses in type 2 diabetes mellitus [32]. Increased levels of HMGB1 have been reported in both diabetic patients and animal models [26, 112]. For all of the above, it is clear that HMGB1 plays a role in the genesis and pathophysiology of IR.

Therapeutic Potential of HMGB1

HMGB1 has been shown to play a significant role in the development of several diseases, particularly CVDs, PE, and IR. Although there are no drugs that target HMGB1 in clinical practice, some anti-HMGB1 agents have been shown to inhibit the expression of HMGB1 in ischemic animal models, including glycyrrhizin [113], ethyl pyruvate (EP) [114], fluvastatin [115], berberine [116], and bleacein [117].

Glycyrrhizin, a glycoconjugated triterpene present in licorice root, exerts protective effects in various diseases, including IR, by suppressing HMGB1 [26]. It also inhibits HMGB1 secretion in the cerebrospinal fluid and serum after stroke, and thereby improves patients' outcomes [118]. Glycyrrhizin also alleviates the aggravation of infarct volume in middle cerebral artery occlusion models [119]. The infarct volume and release of HMGB1 from the cerebral cortex into the serum were attenuated by glycyrrhizin in a focal cerebral ischemia-reperfusion model [104].

EP, a simple aliphatic ester of pyruvic acid, has been shown to have anti-inflammatory effects and confer protective effects in various pathological conditions [120]. EP reduced circulating levels of HMGB1 and significantly prevented lethality [121]. Aspirin, a classical antiplatelet drug, significantly blocked thrombin- and collagen-induced HMGB1 release in active platelets [122]. Two other antiplatelet drugs (clopidogrel and cilostazol) also attenuated the expression of HMGB1 in septic shock [123]. Thus, HMGB1 might serve as a novel target for antiplatelet drugs in thrombotic diseases.

Low-molecular-weight heparin (LMWH) decreased the expression of HMGB1 in inflammation [124]. LMWH was shown to suppress HMGB1 and NETosis, thus suggesting that it might exert a anticoagulant effect by regulating HMGB1-mediated NETosis [125]. In addition, 2-O, 3-O desulfated heparin inhibited HMGB1/RAGE-mediated airway inflammation [126]. In macrophages, 2-O, 3-O desulfated heparin blocked HMGB1 secretion via the inhibition of the activity of acetyltransferase p300 [127]. Thus, HMGB1 might also be a new target for heparin during inflammation and thrombosis.

Similar to heparin, thrombomodulin is another potential drug for DIC. It exhibits its anti-inflammatory effect

by regulating HMGB1. Recombinant soluble thrombomodulin ameliorated cerebral ischemic injury via an HMGB1 inhibitory mechanism in mice with middle cerebral artery occlusion and rats with cerebral vein sinus thrombosis [64, 94]. In a rat model of sepsis, recombinant thrombomodulin suppressed thrombus formation and HMGB1 levels. Moreover, high-dose thrombomodulin tended to increase the bleeding events [128], suggesting that HMGB1 is a target for the antithrombotic effect of thrombomodulin. As vascular endothelial cells are critical in the antithrombotic effect, Bongoni et al. [94] explored the role of thrombomodulin in HMGB1-induced endothelial cell activation. The authors further demonstrated that transgenic expression of thrombomodulin inhibited the activation of endothelial cells via increased HMGB1-induced cleavage [129]. Combining these findings, HMGB1 can be considered to serve as a potential target for the control of CVDs.

Conclusions

HMGB1 and other SI molecules can be actively or passively released from several cells during stress, including hypoxia. Once released into the extracellular space, HMGB1 activates downstream signaling pathway by interacting with its receptors. Elevated levels of HMGB1 are associated with a poor clinical prognosis and outcome in several diseases including CVDs, IR, PE, etc. Currently, drugs are available that specifically target HMGB1. Therefore, the discovery and availability of a novel low-molecular-weight drug or compound will markedly improve the future therapeutic treatment and outcome of CVDs.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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