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REVIEW

Role of High Mobility Group Box 1 in Cardiovascular Diseases

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Abstract— High Mobility Group Box 1 (HMGB1) is a ubiquitous, highly conserved nuclear and cytosolic protein that has diverse biological roles depending on its cellular location and posttranslational modifications. The HMGB1 is localized in the nucleus but can be translocated to the cytoplasm to modulate the intracellular signaling and eventually secreted outside the cells. It is widely established that HMGB1 plays a key role in inflammation; however, the role of HMGB1 in the cardiovascular diseases is not well understood. In this review, we will discuss the latest reports on the pathophysiological link between HMGB1 and cardiovascular complications, with special emphasis on the inflammation. Thus, the understanding of the role of HMGB1 may provide new insights into developing new HMGB1-based therapies.

KEY WORDS: HMGB1; inflammation; cardiovascular; diabetes; angiogenesis.

INTRODUCTION

High Mobility Group Box 1 is a non-histone DNA-binding protein and a member of the High Mobility Group (HMG) protein superfamily. HMG proteins were identified for the first time in 1973 by Goodwin and named according to their high mobility in polyacrylamide gel electrophoresis [1]. HMG proteins are divided in 3 groups: HMGA, HMGB, and HMGN [1]. HMGB1 belongs to the HMGB group, constitutively expressed in the nucleus of almost every cell type, highly conserved in mammalians species, and it is the most studied. HMGB1 knockout mice die shortly after birth due to a severe hypoglycemia, highlighting the importance of HMGB1 in survival [2]. HMGB1 can be actively secreted by activated immune cells including macrophages, monocytes, dendritic cells, epithelial cells, or passively released by dying or injured cells [3–5].

HMGB1 is organized into 3 functional domains, two positively charged DNA-binding domain called Box-A and Box-B and a negatively charged C-terminal acidic domain [6]. Boxes A and B have opposite biological properties: Box A is anti-inflammatory, while Box B is pro-inflammatory and consists of two binding sites for Toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (AGE) [7]. HMGB1 has two nuclear localization sequences (NLS) located in Box-A and between Box-B and the C-terminal region [7]. The acetylation of the lysine residues presents in the NLS leads to the HMGB1 translocation from nucleus to the cytosol and its release. Due to its ability to translocate from the nucleus to the cytosol, HMGB1 can be found in the cytosol, the mitochondria, and on cell membrane

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[8]. In the nucleus, HMGB1 plays a major role in DNA repair, DNA replication, and chromatin structure. In the cytoplasm, HMGB1 acts as a signaling regulator, alarmin, and pro-inflammatory cytokine [9].

It has been reported that significant amounts of extracellular HMGB1 released after cellular activation (monocytes, macrophages, and dendritic cells) through the increased translocation of HMGB1 from the nucleus to cytoplasm or cell death leads to inflammation [10]. The translocation of HMGB1 from nuclear to cytoplasm appears to depend on its acetylation and methylation on lysine residues [11, 12]. Reports showed that not only HMGB1 is released in response to inflammatory stimuli but HMGB1 also triggers a variety of signaling pathways and activate immune cells to release proinflammatory cytokines and chemokines [13]. HMGB1 acts as an inflammatory cytokine under many conditions such as ischemia [14, 15] and seems to depend on the location, the redox state, and the associated signaling pathway involved [16, 17]. HMGB1 has several receptors such the receptors for RAGE, TLR9, TLR4, TLR2, CD24, CXCR4, and others. Only TLR4 and RAGE were extensively studied and confirmed by many investigators [16, 17] RAGE is one of the receptors that binds to HMGB1 and activates smooth muscle cells, immune cells, and the upregulation of RAGE and TLR4 on cells surface. Interestingly, HMGB1 interacts with both TLR4 and RAGE but only its interaction with TLR4 is required for the release of cytokines from macrophages [18].

CARDIAC INFLAMMATION

Cardiac Hypertrophy

Evidence is accumulating that chronic inflammation plays an important role in cardiac diseases. HMGB1 has been associated with many cardiac complications [19, 20]. Inflammation is involved in the progression of pressure overload–induced cardiac hypertrophy and heart failure; however, the mechanisms have not yet been fully determined [21]. It has been reported that HMGB1 expression was increased, during cardiac hypertrophy induced by pressure overload, accompanied with its translocation from the nucleus to the cytoplasm [22]. Moreover, exogenous HMGB1 induces hypertrophy in neonatal ventricular myocytes through calcineurin mechanism [23] while overexpression of nuclear HMGB1 prevents pressure overload–induced cardiac hypertrophy through inhibition of DNA damage mechanism [24]. Human biopsy samples showed a decrease in nuclear HMGB1 expression in failing hearts. The authors also found that nuclear HMGB1 was acetylated and translocated from the nucleus to the cytoplasm during cardiac remodeling. Moreover, cardiac hypertrophy induced by transverse aortic constriction (TAC) was attenuated in HMGB1 transgenic mice suggesting a novel approach to target nuclear HMGB1 in preventing cardiac hypertrophy and improving survival rate in a pressure overload heart failure model [24].

Myocardial Infarction

In a rodent model of myocardial infarction, exogenous HMGB1 has a beneficial effect on post infarct cardiac remodeling via the induction of myocardial regeneration through the induction of resident cardiac c-kit + cell proliferation and differentiation mechanism [25]. The overexpression of HMGB1 seems to protect the heart against myocardial infarction [26]. However, other reports showed that HMGB1 treatment increased infarct size, while mice lacking RAGE were protected from myocardial ischemia reperfusion injury [19].

Myocarditis

Recent reports showed that the immune system plays an important role in the pathology of heart failure [27]. Myocarditis, the leading cause of heart failure in young patients, is defined as an inflammation of the myocardium often leading to cardiomyopathy [28]. The exact mechanism involved in the induction of myocarditis and its progression is not yet fully understood. Studies showed that auto-antibodies to cardiac troponin-I are found in patients with acute coronary syndrome pointing to an early induction of an autoimmune response to troponin-I in these patients [29]. Goser *et al*. are the first to establish a mouse model in which immunization with murine cardiac troponin-I-induced myocardial inflammation, cardiac fibrosis, and heart failure [30]. Using the same murine model of troponin-I-induced experimental autoimmune myocarditis, Bangert *et al*. confirmed Goser *et al.'s* findings that troponin-I immunization induced myocardial inflammation, fibrosis, heart failure, and an increase in serum and myocardial HMGB1 [31]. Interestingly, the inhibition of HMGB1 by glycyrrhizin or anti-HMGB1 antibody reduced troponin-I-induced myocardial inflammation. Moreover, cardiac overexpression of HMGB1-induced cardiac inflammation in both wildtype and RAGE

knockout mice suggests that the pro-inflammatory effect of HMGB1 is independent of RAGE-dependent mechanism. Importantly, RAGE knockout mice, immunized with troponin-I, were protected from cardiac inflammation supporting the concept that HMGB1-induced inflammation is independent of RAGE. Moreover, the authors found that HMGB1 and soluble RAGE levels were elevated in patients with myocarditis suggesting the clinical relevance of HMGB1 and RAGE in cardiac inflammation [31]. Additionally, HMGB1 could contribute to autoimmune myocarditis via a mechanism involving the stimulation of macrophage reprogramming toward a pro-inflammatory M1-like phenotype [32].

Heart Failure and Cardiac Fibrosis

Interestingly, high level of HMGB1 has been observed in patients with heart failure [33] suggesting the potential importance of HMGB1 in heart failure. Interestingly, cardiac-specific deletion of HMGB1 using c-TNT-CRE mouse system resulted in cardiomyopathy which further led to heart failure and impaired body growth [34]. The deletion of HMGB1 in cardiomyocyte was associated with low blood glucose and changes in inflammatory genes, glucocorticoid receptor's function, and glycolipid metabolism [34]. These findings might explain why the deletion of HMGB1 in mice die prematurely of severe hypoglycemia [2]. Cardiac fibrosis is another feature of heart disease. In a mouse model of cardiac fibrosis induced by isoproterenol infusion, Wu et al. showed that the interaction between HMGB1 and TLR2 contributes to cardiac fibrosis via the suppression of autophagy in cardiac fibroblasts [35]. The authors also found that Glycyrrhizin acid, an inhibitor of HMGB1, alleviates cardiac fibrosis through the abrogation of HMGB1-TLR2 interaction [35]. Together, the understanding of HMGB1 mechanism in heart diseases is important to develop a potential therapy to prevent and/or stop the progression of heart diseases.

VASCULAR INFLAMMATION

Kawasaki Disease

Kawasaki disease (KD) is a juvenile autoimmune acute vasculitis disease and is the leading cause of pediatric cardiac disease [36]. It is well-established that KD affects small and medium arteries, especially coronary arteries leading to myocardial infarction, aneurysm, and stenosis. Whether HMGB1 plays a critical role in KD-induced vasculitis was the interest of many studies. First, it has been reported that children with KD exhibit a high level of HMGB1 in comparison to healthy children [37]. In line with these findings, Qian et al. confirmed that the expression of HMGB1/sRAGE/NFκB axis was elevated in the serum of children with KD as well as in an animal model of KD [38]. The authors also found that HMGB1, RAGE, and NFκB were localized in the endothelial cells of coronary arteries supporting the concept that endothelial cell inflammation is a key factor in coronary artery remodeling, aneurysm, and coronary vasculitis [38]. It is well-established that HMGB1 can mediate the pro-inflammatory response of endothelial cells and induce apoptotic, autophagic, and pyroptotic cell death, which is a form of proinflammatory cell death that combines features of both apoptosis and necrosis and can be mediated by inflammasome-dependent caspase-1 activation leading to the activation of Gasdermin D, IL-1β, and IL-18. Interestingly, previous studies showed that HMGB1 was able to induce macrophage pyroptosis via RAGE signaling. Also, recent studies using a mouse model of KD as well as *in vitro* data elucidated that HMGB1 released by immune cells triggered HMGB1-RAGE signaling pathway in endothelial cells leading to the activation of cathepsin B and consequently endothelial cells pyroptosis via NLRP3 inflammasome. These results indicate the importance of endothelial cell inflammation-induced pyroptosis in the pathology of KD HMGB1-dependent mechanism [39]. These findings were supported by recent study showing that HMGB1 plays a critical role in the development of KD pathogenesis [40]. Although the role of HMGB1 in KD-induced vasculitis is well described, further studies should delineate the full mechanism by which HMGB1 is involved in this vascular pathology for a potential therapeutic approach.

Angiogenesis

Mitola et al. were the first to document that extracellular HMGB1 induces angiogenesis in endothelial cells [41]. Using an *in vitro* model of angiogenesis, the authors showed that HMGB1 stimulates chemotaxis, increases endothelial cell motility, and triggers the formation of endothelial cell sprouting. Supporting the concept about the role of HMGB1 in angiogenesis, HMGB1 also induced neovascularization in a chick embryo CAM model. Interestingly, blocking RAGE inhibits the capacity of HMGB1 to induce endothelial proliferation as well

as neovascularization in the chick embryo CAM. These data suggest that HMGB1-induced angiogenesis is mediated by RAGE mechanism. However, HMGB1 can bind to LTRs and Syndecan-1, both known to be involved in angiogenesis [42, 43], which may suggest the potential mechanism that LTRs and Syndecan-1 are signaling pathways to HMGB1 in the regulation of angiogenesis.

It is well documented that HMGB1 promotes recovery from muscle ischemia [44, 45]. In fact, HMGB1 is required for endothelial tube formation *in vitro* and increases vascular density in ischemic skeletal muscles [44]. A link between autophagy, inflammasome, and HMGB1 release has been proposed as a mechanism to promote muscle recovery from ischemic injury [46, 47]. Xu et al. confirmed that HMGB1 is prominently expressed in muscle from patients with peripheral artery disease and that in the setting of ischemia, the inhibition of autophagy by chloroquine regulates the mobilization of HMGB1 from the nucleus into the extracellular space promoting a better recovery from ischemic injury [47].

Recently Lan et al. [48] proposed that the internalization of HMGB1 in endothelial cells is a new mechanism by which HMGB1 promotes angiogenesis mediated by dynamin and RAGE and the release of VEGF. The authors also validated their finding *in vivo* using a murine model of hind limb ischemia-induced angiogenesis showing that HMGB1 internalization in endothelial cells occurred *in vivo*. Although, the study supports the role of HMGB1 in ischemia-induced angiogenesis and sheds light on a new mechanism by which HMGB1 stimulates angiogenesis through its internalization by endothelial cells, the authors only used human umbilical vein endothelial cells (HUVECs) as an *in vitro* model for angiogenesis. HUVECs are isolated from large vein and might have different signaling for angiogenesis when compared to endothelial cells from the microcirculation [48]. Therefore, HMGB1 internalization–induced angiogenesis still needs to be investigated in endothelial cells isolated from the microcirculation. While the involvement of RAGE activation in HMGB1-induced angiogenesis is widely known, the role of RAGE in angiogenesis is controversial. For instance, Lan et al. [48] showed that blood flow measurements were identical between C57BL6 and RAGE knockout mice after hind limb ischemia. Other investigators showed that RAGE knockout mice exhibit an increase in the perfusion ratio and number of capillaries when compared to C57BL6 mice [49].

Another important aspect worth to mention is the internalization of HMGB1 in endothelial cells during arteriogenesis or collateral growth in response to ischemia. Activated vascular smooth muscle cells (VSMCs) are also known to produce HMGB1 [50]. Arteriogenesis is a process that requires VSMC migration and proliferation dictated by HMGB1. Therefore, would VSMCs also use HMGB1 internalization as a mechanism to promote arteriogenesis? What is the status of HMGB1 internalization in pathological condition such as ischemic diseases?

Atherosclerosis

Early report indicated that HMGB1 plays a critical role in the development of atherosclerosis through pro-inflammatory factors and immune cell mechanism [51]. Recent reports showed that mice lacking endothelial HMGB1 are protected from developing atherosclerosis, a major cardiovascular disease, which includes inflammation [52]. The authors demonstrated that transcytosis of low-density lipoprotein across endothelial cell, critical in the development of atherosclerosis, depends on HMGB1 role in the nucleus by prolonging the half-life of sterol regulatory element-binding protein 2 essential to the production of scavenger receptor class B type 1 [52]. The role of HMGB1 in atherosclerosis is supported by studies from Dr. Zhang's laboratory [53]. The authors demonstrated that inhibiting the HMGB1 with glycyrrhizic acid reduced the intimal thickness of carotid artery and plaque formation in rat with diabetic atherosclerosis [53]. The protective effect of HMGB1 inhibition against atherosclerosis is through the inhibition of macrophages and inflammation [53]. In a recent study, it has been reported that HMGB1 is a direct target of miR-141-5p, which is downregulated in atherosclerosis [54]. The overexpression of miR-141-5p decreases the inflammation and abnormal proliferation and migration of VSMCs in the setting of atherosclerosis through the reduction in HMGB1 and NFkB expression [54]. As described in the Introduction, HMGB1 binds to a variety of receptors including the TLR4, which are involved in the development of atherosclerosis [55]. The inhibition of HMGB1 protects against atherosclerosis by blunting the production of pro-inflammatory cytokines and upregulating PPARg/LXRa-ABCA1 through TLR4 [55]. Together, the two studies [48, 52] indicate that HMGB1 is needed for the induction of angiogenesis in the setting of ischemia but its effect in atherosclerosis is still controversial. This aspect is worth to mention in order to understand the versatile role of HMGB1 in vascular pathologies. The data

reported by Lan et al. [48] shed new lights into a novel mechanism of action of HMGB1 in endothelial cells to stimulate angiogenesis. Further studies are needed to unravel the mechanism by which HMGB1 from other cells such as microvascular endothelial cells and VSMCs, and macrophages to stimulate angiogenesis/arteriogenesis. The reported findings open new avenues to enhance our understanding about the beneficial effect of HMGB1 and the potential therapeutic approach in the setting of cardiovascular diseases.

DIABETES

Diabetes is an endemic, chronic disease, and its prevalence is increasing worldwide. During the past decade, inflammation emerges as a key feature of obesity and type 2 diabetes. In fact, obesity, metabolic syndrome (MetS), and diabetes are characterized by low-grade chronic inflammation and an increase in HMGB1 release [56, 57]. Several studies have shown the relation between HMGB1 and diabetes mellitus (DM). Diabetic patients exhibit higher serum HMGB1 compared to non-diabetic patients and been shown to be associated with glucose metabolism and body mass index [58]. In a recent case–control study, children with type 1 diabetes exhibit higher level of HMGB1 compared to control group suggesting the possible involvement of HMGB1 in the etiology of type 1 diabetes [59]. Moreover, Yan et al. showed an increase in HMGB1 serum level in type 2 diabetic patients with coronary arteries disease (CAD) *versus* type 2 diabetic without CAD [58]. These data indicate that HMGB1 could be a common mechanism involved in the development of type 1 and type 2 diabetes.

Moreover, using a model of middle cerebral artery occlusion-reperfusion (MCAO/Re) Wang et al. showed that HMGB1 secretion increased in the brain of diabetic compared to non-diabetic rat [15]. The authors also found that ischemia induces an increase in the secretion of HMGB1 in diabetic rats highlighting the importance of targeting HMGB1 as a therapy for post ischemic injury in diabetic patients [15]. Interestingly, HMGB1 level is increased in muscle tissue and serum of patients with peripheral artery disease (PAD). Moreover, HMGB1 plasma levels were correlated with the severity of PAD [60, 61]. Conversely, HMGB1 seems to be involved in tissue repair after peripheral ischemia [62]. In diabetic animal models of hind limb ischemia, HMGB1 protein expression was lower in the ischemic tissues and the administration of HMGB1 restored the blood flow recovery and improved neovascularization through VEGF mechanism [62]. Furthermore, the secretion of HMGB1 from activated macrophages enhanced the release of VEGF, TNFα, and IL-8 promoting the mobilization of endothelial progenitor cells to stimulate angiogenesis [62]. Moreover, hyperglycemia stimulates HMGB1 release leading to vascular dysfunction via ROS (32, 40) and RAGE-NFκB axis [63].

Diabetic cardiomyopathy is a chronic heart complication seen in diabetic patients that occurs independently from coronary artery diseases and hypertension. The treatment of cardiac fibroblasts, macrophages, and cardiomyocytes with high glucose level led to the induction of HMGB1 expression and an increase in the NFκB binding activity, IL-6, and TNFα level [63]. Moreover, these *in vitro* data were validated in a murine model of type 1 diabetes induced by streptozotocin and subjected to myocardial infarction. After myocardial infarction, mice exhibit higher levels of HMGB1 in the myocardium and in the circulation. Interestingly, HMGB1 blockade significantly reduced post myocardial infarction remodeling and cardiac damages through the involvement of ERK1/2, JNK, and NFκB signaling [63]. In line with these findings, the authors conducted a clinical pilot study in diabetic patients with a history of myocardial infarction. HMGB1 plasma levels were higher in diabetic patients compared to healthy controls and were negatively correlated with cardiac performance [63]. Together, these data indicate that HMGB1 is an important mechanism in the etiology of diabetes and in the cardiovascular complications related to diabetes.

Vascular calcification is a common vascular complication associated with age and diabetes, and characterized by the transformation of vascular smooth muscle cells to osteo/chondrocyte cells [64]. Studies in animal models and patients documented the association between HMGB1 and aortic valve calcification [65]. Patients with aortic valve calcification have an increase in tissue and plasma level of HMGB1 [65] as well as an accumulation of HMGB1 extracellularly in areas associated with macrophage infiltration and calcification in calcific aortic valve stenosis [66]. Recent reports showed that HMGB1 mediates high glucose-induced calcification in VSMCs of saphenous vein via the activation of NFκB and the induction of BMP2 expression in VSMC [67]. A recent study in a mouse model of type 1 diabetes showed that diabetes induced HMGB1 secretion via the induction of endoplasmic reticulum (ER) stress leading to vascular

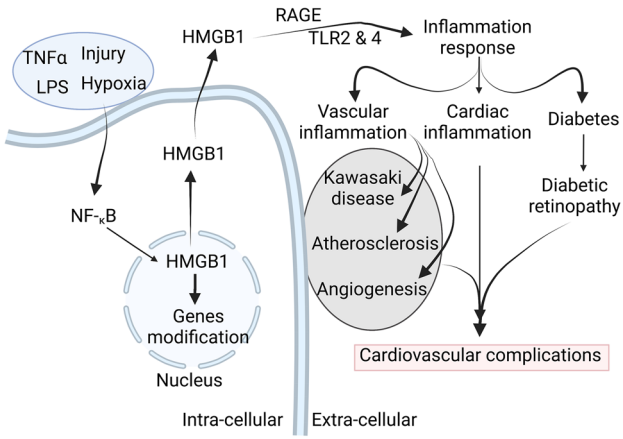
calcification [68]. Interestingly, the authors found that the inhibition of HMGB1 and ER stress alleviates vascular calcification in Streptozotocin-induced diabetic mice. Moreover, AGEs induce the translocation and secretion of HMGB1 from VSMCs through the ER stress. Runx2 is a transcription factor involved in the pathology of vascular calcification [69–71]. In fact, HMGB1 has been shown to upregulate the expression of Runx2 in VSMCs via the ER stress [68] suggesting the implication of HMGB1 in cardiovascular calcification through ER stress–dependent mechanism. TGFβ/BMP signaling are important players in calcification. Interestingly, recent findings showed that HMGB1 regulates the expression or release of TGFβ and BMP2 suggesting its importance in cardiovascular calcification. Inflammation, oxidative stress, and autophagy signaling were documented as mechanisms by which HMGB1 promotes cardiovascular calcification [64]. All these data indicate that HMGB1 is not just important in inflammation-induced pathology but also critical in structural remodeling.

Diabetic Retinopathy

Diabetic retinopathy is a common complication of diabetes mellitus and the leading cause of blindness in adults. Increasing evidence has indicated that HMGB1 plays a central role in the pathogenesis of diabetic retinopathy [72, 73]. HMGB1 expression was found to be upregulated in the serum of patients with diabetic retinopathy with a positive correlation between serum and vitreous levels of HMGB1 [74]. *In vitro* studies using human retinal endothelial cells, Chip sequencing, and luciferase assay showed the interaction between IκB-α and HMGB1 and demonstrated that HMGB1 was involved in the pathogenesis of diabetic retinopathy via the NFκB pathway [75]. Moreover, Abu El-Asrar et al. showed a link between HMGB1 and different marker of oxidative stress in the pathogenesis of inflammation and neovascularization in diabetic retinopathy [76]. The exchange protein activated by cAMP (Epac) has been shown to regulate HMGB1 expression in retinal vasculature through AMPK and SIRT1 pathway in the setting of diabetes [77–79]. Moreover, the inhibition of the release of HMGB1 using Glycyrrhizin reduces HMGB1 levels in the retinas as well as diabetic-induced damage to the retinas associated with reduced reactive oxygen species, TNFα and IL1β [80]. These data indicate the importance of targeting HMGB1 to stop the progression of diabetes-induced retinopathy.

THERAPEUTIC TARGET FOR CARDIOVASCULAR COMPLICATIONS

Coronary artery diseases (CAD) are the leading cause of morbidity and mortality worldwide. Diabetes mellitus is considered to be an independent risk factor in the development of CAD. Metformin, an antidiabetic drug, has been shown to lower cardiovascular complications in diabetic patients [81]. Previous study showed that metformin has anti-inflammatory properties due to the inhibition of pro-inflammatory cytokine production as well as the inhibition of HMGB1 release likely through AMPK-mechanism [82]. Recent study reported that metformin inhibits HMGB1 translocation from the nucleus to the cytosol and therefore limiting HMGB1 in the nucleus and blocking its release through the direct binding of metformin to the C-terminal acidic tail of HMGB1 [82–84]. Moreover, other studies strengthen the concept that metformin protects the heart against hyperglycemia-induced injury via the inhibition of HMGB1/RAGE expression [85]. These studies opened new avenues to understand how metformin inhibits inflammation by targeting HMGB1, which will be clinically significant. Glycyrrhizin, a natural anti-inflammatory compound, found in licorice that inhibits HMGB1 activities via a direct binding to HMGB1 [86] has been shown to protect against ischemia reperfusion injury in rat brains through the reduction of the release of HMGB1 into the extracellular space as well as blocking its activity [87]. Moreover, Glycyrrhizin inhibits HMGB1 expression and its signaling pathways in diabetic retinopathy [88, 89]. Recent reports by Dandona et al. showed that insulin infusion in type 1 diabetic patients suppressed HMGB1 expression in monocytes [90]. Resveratrol, an antioxidant compound, has been found to prevent the occurrence of diabetic cardiomyopathy by decreasing HMGB1 expression in the left ventricular myocardium of type 1 diabetic rats [91, 92]. Astilbin, another antioxidant, has been shown to provide cardio-protection against ischemia reperfusion injury in diabetic rat through the manipulation of HMGB1/NFκB axis [93]. ACE inhibitors also inhibit cardiac inflammation via the reduction of the release of HMGB1 [94]. It is important and clinically relevant to understand the molecular mechanism of induction as well as the release of HMGB1 in diseases associated with inflammation for an efficient potential therapy.



Scheme 1 Schema Graphical representation illustrating the role of HMGB1 in cardiovascular complications

CONCLUSION

The detrimental and beneficial effect of HMGB1 in the setting of different cardiovascular diseases is very intriguing (Scheme 1). The translocation of HMGB1 from nucleus to cytoplasm plays a key role in inflammation. We believe that in order to develop an efficient therapeutic strategy targeting HMGB1, the approach should modulate the level of the HMGB1 in a cell-specific manner with a special focus on the localization of HMGB1.

Table 1 The Mechanism of HMGB1 in Cardiovascular Complications

HMGB1	Involvement	Signaling/Markers/Mechanism	Reference
Cytosol	Cardiac hypertrophy and heart failure	Increase HMGB1 expression and translocation from nucleus to cytoplasm and intercellular space	[22]
Not specify	Cardiac hypertrophy	Calcineurin	[23]
Nucleus to cytoplasm	Cardiac remodeling	HMGB1 acetylation and translocation from the nucleus to the cytoplasm	[24]
Not specify	Myocardial regeneration	Resident cardiac c-kit + cell proliferation and differentiation	[25]
Not specify	Myocardial inflammation	Troponin-I	[31]
Not specify	Autoimmune myocarditis	Pro-inflammatory M1	[32]
Not specify	Cardiac fibrosis	TLR2 and autophagy	[35]
Not specify	Kawasaki disease	sRAGE/NFκB	[38]
Not specify	Kawasaki disease	RAGE/cathepsin B/NLRP3 inflammasome	[39]
Not specify	Angiogenesis	RAGE/LTRs/Syndecan-1	[42, 43]
Not specify	Angiogenesis	Dynamin/RAGE/VEGF	[48]
Not specify	Angiogenesis	VEGF/TNFα/IL-8	[62]
Nucleus	Atherosclerosis	Sterol regulatory element-binding protein 2/receptor class B type 1	[52]
Not specify	Diabetic atherosclerosis	Macrophages and inflammation inhibition	[53]
Not specify	Atherosclerosis	TLR4/PPARγ/LXRa-ABCA1	[55]
Not specify	Vascular dysfunction in diabetes	ROS/RAGE/NFkB	[32, 40, 63]
Not specify	Myocardial infarction remodeling	ERK1/2/JNK/NFkB	[63]
Not specify	VSMC calcification	HMGB1 regulates the expression of TGFβ, BMP2, and autophagy, activates NFκB, and upregulates Runx2 and oxidative stress	[64, 67, 68]
Not specify	Diabetic retinopathy	NFkB/reactive oxygen species/TNFα and IL1β	[75, 80]

Further studies are necessary to understand the mechanisms by which extracellular and nuclear HMGB1 affects cardiac and vascular inflammation and repair/regeneration and how it can be manipulated to maximize its therapeutic potential in cardiovascular diseases. Summary of HMGB1 roles and mechanisms in cardiovascular complications are represented in Scheme 1 and Table 1.

AUTHOR CONTRIBUTION

All authors made substantial contribution to the present review. Dr. Matrougui wrote and edited the manuscript. Dr. Belmadani wrote and edited the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

DECLARATIONS

Ethics Approval and Consent to Participate (Human Ethics, Animal Ethics or Plant Ethics) Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

Disclaimer All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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