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Dual faced HMGB1 plays multiple roles in cardiomyocyte senescence and cardiac inflammatory injury

Hongxiang Lu[a,b,1], Zhenzhen Zhang[c,1], Prince Amoah Barnie[a,b,1], Zhaoliang Su[a,b,*]

[a] International Genome Center, Jiangsu University, Zhenjiang, 212013, China
[b] Department of Immunology, School of Medicine, Jiangsu University, Zhenjiang, 212013, China
[c] Naval Medical Institute of PLA, Shanghai, China

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ABSTRACT

High mobility group box 1 (HMGB1) is constitutively expressed by many cells. In cells, HMGB1 is a transcription factor or transcription enhancer that is involved in nucleosome sliding, DNA repair, V(D)J recombination, telomere homeostasis, autophagy and viral sensing. HMGB1 can also be secreted or released by stressed cells and serves as an alarmin, cytokine or growth factor to activate the immune response. This protein facilitates $CD4^+$ T cell differentiation and tissue repair through binding with its receptors, including toll-like receptors (TLRs) and the receptor for advanced glycation end-products (RAGE). Recent works have established that HMGB1 plays many vital functions in cardiac inflammatory injury, cardiac regeneration and remodelling. The present review addresses the novel role of HMGB1 in secretion and cardiomyocyte senescence and in the dual faced roles of HMGB1 in cardiac inflammatory injury, inflammatory resolution and cardiac regeneration and remodelling following cardiac injury.

Specifications Table

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More specific subject area	*Immunology-cytokine*
Type of data	*text file and figure*
How data was acquired	*summary*
Data format	*Figure*
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1. Introduction

High-mobility group box 1 (HMGB1) is a highly conserved DNA shepherding protein that is ubiquitously expressed in almost all cells. Generally, HMGB1 is located in the nucleus, but it can also translocate to the cytoplasm and the extracellular microenvironment during cell activation, injury or death. Extracellular HMGB1 can be actively secreted from multiple cell types during stress, including macrophages, monocytes, natural killer cells (NK), dendritic cells (DCs), endothelial cells, fibroblasts, cardiomyocytes, cancer cells and platelets, or it be passively released from necrotic or damaged cells [1]. However, the biological activity of HMGB1 depends on its location, context and post-translational modification [2]. For example, in the nucleus, it acts as a nuclear DNA chaperone that takes part in DNA replication, transcription, V(D)J recombination, repair, and chromatin stability, and it regulates the transcriptional activity of p53, nuclear factor (NF)-κB, steroid hormone receptors and glucocorticoid receptors [3,4]. HMGB1 can regulate the number of ribosomes and their activity [5]. In the cytoplasm, HMGB1 regulates autophagy and apoptosis [6]. However, extracellular HMGB1 can serve as a damage-associated molecular pattern (DAMP) or alarmin to activate immune responses, play key roles in cell differentiation and development, facilitate the development of inflammation, cancer and autoimmune disease and facilitate microvascular rolling and adhesion through engagement with its cell-surface

Abbreviations: ANG II, angiotensinII; CaMK, calcium/calmodulin-dependent protein kinase; CTF2, CCAAT-binding transcription factor 2; DCM, dilated cardiomyopathy; EAM, experimental autoimmune myocarditis; ECM, extracellular matrix; HDAC, histone deacetylase; HMGB1, high mobility group box 1; I/R, ischemia/reperfusion; MFG-E8, milk fat globule EGF factor 8; PARP, poly(ADP)-ribose polymerase; PS, phosphatidylserine; RAGE, receptor for advanced glycation end-products; SASP, senescence-associated secretory phenotype; SIRT1, sirtuin-1

* Corresponding author at: Department of Immunology, School of Medicine, Jiangsu University, 301 Xuefu Road, Zhenjiang, Jiangsu, China.
E-mail address: szl30@ujs.edu.cn (Z. Su).

[1] These authors contributed equally.

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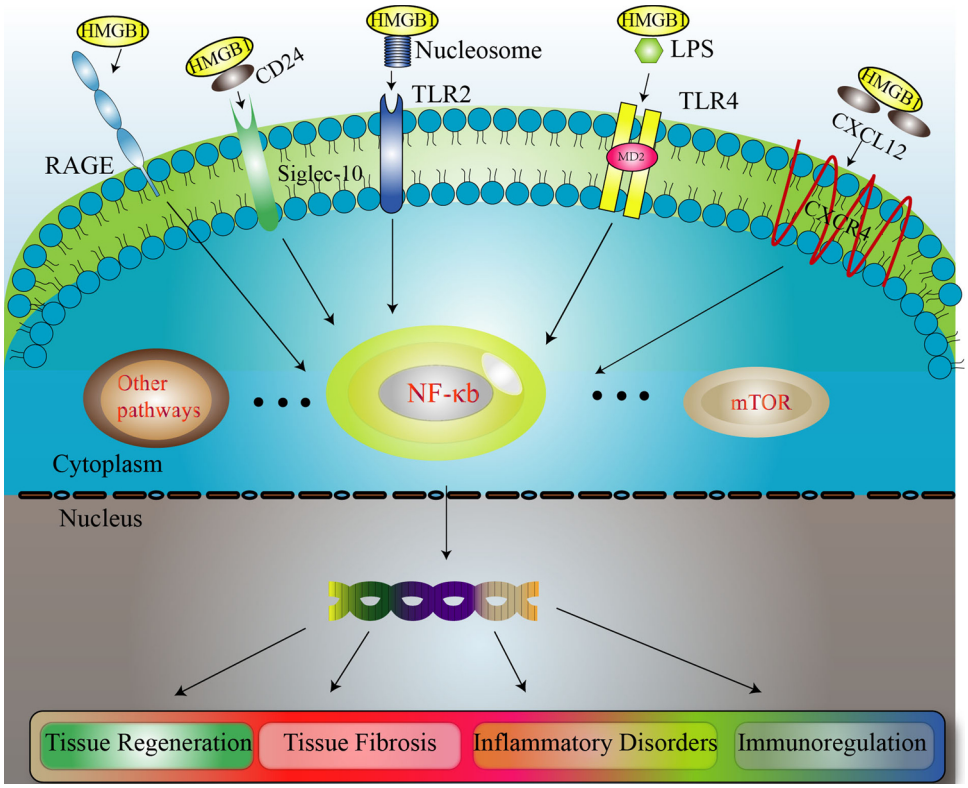

Fig. 1. The multiple roles of HMGB1. HMGB1 binds with RAGE, TLRs, CD24/Siglec-10, Mac-1, thrombomodulin, CXCR4 or single transmembrane domain proteins (e.g., syndecans). It activates NF-κB, mTOR and other pathways and is involved in tissue regeneration, organ fibrosis, immunoregulation, autophagy and inflammatory disorders.

receptors on cells [7–9]. Additionally, HMGB1 can also promote tissue regeneration [10] and organic fibrosis [11]. Furthermore, HMGB1 has also been documented to play integral roles in the pathogenesis of chronic inflammatory-mediated cardiac diseases including chronic myocarditis, which is a chronic inflammatory disorder that involves ventricular remodelling, hypertrophy and fibrosis (Fig. 1) [12]. However, there are some controversial data that indicate that HMGB1 has cardioprotective properties [13]. Therefore, the present review will focus on the recent research regarding HMGB1 secretion, HMGB1 as a determinant of cell fate and the dual faced roles of HMGB1 in cardiac inflammatory injury, inflammatory resolution, and in cardiac regeneration and remodelling after cardiac injury.

2. The general characteristics of HMGB1

2.1. HMGB1 structure

HMGB1 contains 215 amino acids and has a tripartite structure consisting of two DNA-binding domains, the A box (amino acid residues 9–79) and B box (amino acid residues 95–163), and a C-terminal tail domain that is negatively charged and is composed exclusively of 30 glutamic and aspartic acids [14]. The A and B boxes can bind DNA, and the C-terminal region can bind to histones; the C-terminal region can also interact with the A and B boxes, modifying the 3-dimensional structure of HMGB1 and its molecular interactions [15]. Additionally, the C-terminal acidic tail is suggested to play an indispensable role in regulating DNA binding and DNA damage repair and is responsible for the inhibitory effects of HMGB1 on efferocytosis [16]. Unlike histones, HMGB1 binds to DNA with low affinity and can move from the nucleus to the cytoplasm depending upon the cell cycle phase [17]. HMGB1 shows preferences for certain DNA structures, such as bends or cruciform, consistent with a role in modifying nucleosomal structure to regulate transcription, recombination or repair [18].

2.2. HMGB1 isoforms

HMGB1 contains three redox-sensitive cysteine residues (C23, C45, and C106) in the A and B box. C23 and C45 can form an intramolecular disulphide bond, whereas C106 is unpaired and is essential for interaction with ligands such as TLR2/4 [19]. According to the redox status of the three cysteine residues, HMGB1 can be modified into three isoforms, termed all-thiol HMGB1, disulphide HMGB1 (partially oxidized), and oxidized HMGB1 [20,21] (Fig. 2). All-thiol HMGB1 is known to bind to other chemokines (e.g., CXCL12) and stimulates leukocyte recruitment via the CXCR4 receptor [22]. All-thiol HMGB1 can also promote the regeneration of multiple tissues by transitioning stem cells to GAlert or through the CXCR4 receptor pathway [10,23]. Disulphide HMGB1 has the ability to activate immune cells to produce cytokines/chemokines via TLR2/4 or other receptors such as RAGE [22,24], TLR9, cluster of differentiation 24 (CD24)/Siglec-10 [24], Mac-1, thrombomodulin [25], or single transmembrane domain proteins (e.g., syndecans) (Fig. 1) [20]. Structure-function studies have shown that the extracellular cytokine activities of HMGB1 reside within the B box. However, the cytokine role of the B box can be competitively inhibited by the specific HMGB1 antagonist, truncated A box protein [26].

2.3. Regulation of HMGB1 expression

As a housekeeping gene, HMGB1 is ubiquitously expressed by almost all cells. However, the expression level correlates with the differentiation stage of cells, such as low in differentiated cells, and high in undifferentiated cells [27]. HMGB1 expression is regulated at three levels: transcription, translation, stability of the mRNA and protein itself. HMGB1 is a compact gene, its transcription is at the two-cell stage in mice. HMGB1 has a TATA-less promoter in human, however, a silencer target on upstream of the promoter will reduce HMGB1 transcription. Conversely, the enhancer can increase HMGB1 transcriptional activity [28]. Additionally, p53, CCAAT-binding transcription factor 2 (CTF2) and JAK/STAT are also involved in regulation of HMGB1 expression [3,4].

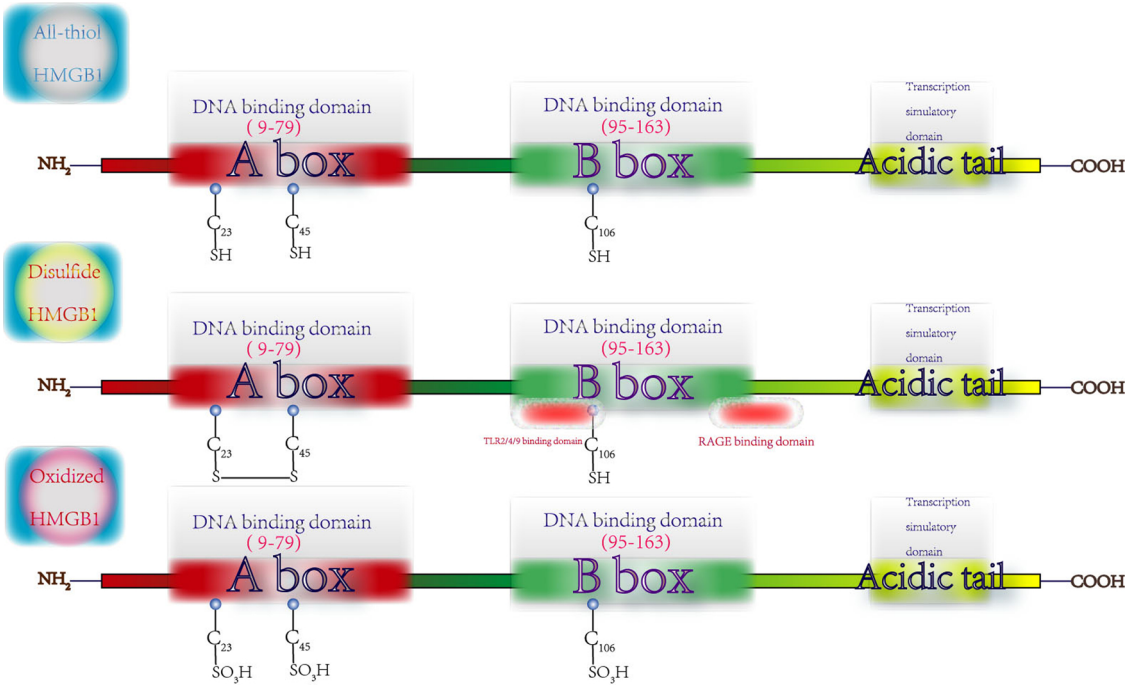

Fig. 2. The structure and isoforms of HMGB1. HMGB1 contains three redox-sensitive cysteine residues (C23, C45, and C106) in the A and B box. According to the redox status of the three cysteines, HMGB1 can be modified into three isoforms, which are termed all-thiol HMGB1, disulphide HMGB1 (partially oxidized), and oxidized HMGB1. The B box has cytokine activities; however, the A box can competitively inhibit B box activities. The C-terminal acidic tail is the transcriptional modulation region.

3. HMGB1 shuttle and cellular senescence

Interestingly, under stress, HMGB1 shuttles continually between the nuclear and cytoplasmic compartments in a tightly regulated way [29,30]. HMGB1 shuttling or translocation is linked with cellular senescence. Cellular senescence is an irreversible arrest of the cell cycle that occurs when cells are at the end of their replicative potential or under stress, for example, oxidative stress, DNA damage, irradiation or oncogenic activation.

Generally, cellular senescence is considered a protective response that can inhibit cancer development and limit the extent of organic fibrosis. However, excessive accumulation of senescent cells leads to detrimental consequences, such as age-related disease [31]. HMGB1 plays multiple roles in the cell, such as contributing to nucleosome formation, increasing the affinity of transcriptional factors for the chromosome, and stabilizing DNA during replication and repair in nucleus. However, HMGB1 can redistribute or re-localize to the extracellular milieu in senescent cells. The HMGB1 shuttle induces a p53-dependent cellular senescence. Therefore, the HMGB1 shuttle has been considered a marker of senescent cells [31–33]. Furthermore, extracellular HMGB1 can stimulate inflammatory cytokine secretion through TLR2/4 and NF-κB signalling and precedes senescence-associated secretory phenotype (SASP) production, which is a hallmark of cellular senescence [34,35].

4. HMGB1 release

4.1. Active secretion of HMGB1 is extensive existence

HMGB1 can be passively released by damaged, primary or secondary necrotic cells as well as apoptotic cells [36]. HMGB1 released by necrotic cells has cytokine activity; however, if released by apoptosis, it has a tolerogenic characteristic [37]. During apoptosis, HMGB1 is oxidized by C106, which limits HMGB1 binding to different partners and/or receptors. Additionally, C106 locates the B box, which can also explain the lack of cytokine activity. Previous data demonstrated that HMGB1 can also be actively secreted by macrophages or DCs [38]. However, many non-immune cells can also actively secrete HMGB1 under stress; for example, platelet-derived HMGB1 not only is a critical mediator of thrombosis but also supports bacterial clearance [39,40]. MCF-7 cell-derived HMGB1 contributes to breast cancer development by supporting M-MDSC differentiation from bone marrow progenitor cells and facilitating conversion of monocytes into MDSC-like cells [41]. Furthermore, cardiomyocytes and cardiac fibroblasts can secrete HMGB1, and HMGB1 can promote cardiac injury or cardiac fibrosis [42,43]. The active secretion of HMGB1 is extensive existence, and HMGB1 derived from different cells has specific biological activities.

4.2. Post transcriptional modifications and active secretion of HMGB1

Active secretion of HMGB1 requires relocation of the protein from the nucleus to the cytosol or lysosomal compartment and limitation of newly synthesized HMGB1 nuclear re-entry by post-translational modifications, such as methylation, phosphorylation, and acetylation [44–47]. HMGB1 does not contain a secretory leader peptide; therefore, HMGB1 secretion is not dependent on the classical endoplasmic reticulum (ER)-Golgi pathway but instead on a dedicated unconventional secretory pathway [48,49]. The active secretion of HMGB1 requires relocation from the nucleus, which is associated with post-translational modifications of lysine or serine residues and prevents nuclear localization [45]. For example, calcium/calmodulin-dependent protein kinase (CaMK) IV-dependent serine phosphorylation of HMGB1 contributed to the HMGB1 shuttle [50]. Acetylation of lysine residues also plays a critical role in HMGB1 secretion, which facilitates HMGB1 accumulation in secretory lysosomes. Hyperacetylation of lysine residues not only increases the activity of acetyltransferases but also decreases the activity of deacetylase enzyme histone deacetylase (HDAC) 1, 4 and 5 [51,52]. Sirtuin-1(SIRT1) dissociates from HMGB1 during shuttling from the nucleus to the cytosol and promotes the acetylation of HMGB1 [53,54]. Although the translocation of HMGB1 into the cytosol requires post-translational modifications, there are other factors involved in the process. For example, following DNA-alkylating damage, poly(ADP)-

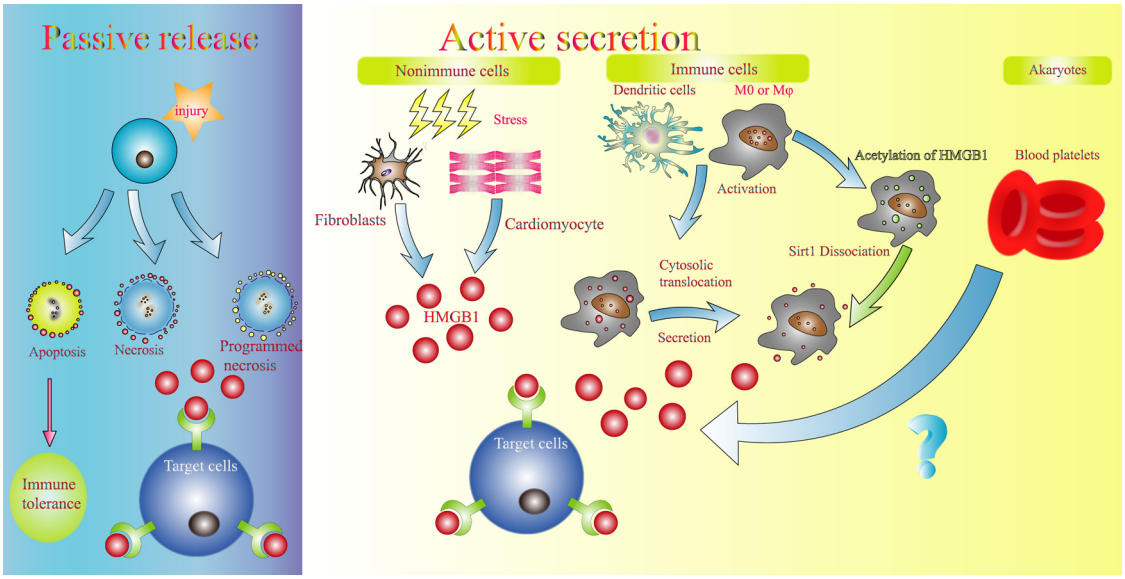

Fig. 3. Secretion or release of HMGB1. HMGB1 can be passively released by apoptosis, necrosis or necroptosis. However, only HMGB1 from necrosis and necroptosis can induce biological activities. HMGB1 can also be actively secreted by cardiac fibroblasts, cardiomyocytes, dendritic cells or macrophages, as well as platelets. HMGB1 secreted by nucleated cells is mainly independent of the ER-Golgi pathway. Conversely, deacetylase enzymes HDAC 1, 4 and 5, SIRT1, and post-translational modifications are involved in this process. However, the detailed mechanism of HMGB1 secretion by platelets remains unclear.

ribose polymerase (PARP) is required for HMGB1 to translocate from the nucleus to the cytosol [55]. Of course, other secretion mechanisms may be existence, such as platelet-derived HMGB1. As is known, platelets do not have a nucleus; thus, there is no translocation from the nucleus to the cytosol in these cells (Fig. 3).

5. HMGB1 and cardiac injury

5.1. HMGB1 in inflammatory development following cardiac injury

HMGB1 was proposed to link cardiomyocyte necrosis, necroptosis or apoptosis following cardiac injury in myocardial infarction induced by ischaemia/reperfusion (I/R) injury and myocarditis [56]. However, the effects of HMGB1 on cardiomyocyte necrosis, necroptosis and apoptosis are still controversial. For example, some research has shown that HMGB1-enhanced cardiomyocyte apoptosis contributed to myocardial I/R injury and hyperglycaemia development [57,58]. Conversely, Narumi et al. showed that intracellular HMGB1 attenuated doxorubicin-induced cardiomyocyte apoptosis [58]. Furthermore, Lin et al. showed that HMGB1 cannot change the expression of total or cytosolic Bax in cardiomyocytes, which indicates that HMGB1 does not increase mitochondrial translocation of Bax or cardiomyocyte apoptosis [59]. However, these differences may be caused by the HMGB1 source or HMGB1 modification. Furthermore, research has also indicated that HMGB1 is an autophagy sensor [60,61]. ROS produced from heart injury can increase HMGB1 translocation from the nucleus to the cytosol and thereby enhance autophagic flux [60], which implies that HMGB1 translocation induces autophagy after prolonged cellular stress. Therefore, we can speculate that HMGB1 is detrimental for cardiomyocytes during initial stages of cardiac injury.

HMGB1, as a critical inflammatory factor, can promote inflammatory cytokine production, recruit inflammatory cell infiltration and modulate lymphocyte activation, polarization or differentiation by acting on potential receptors that result in tissue damage [62]. However, accumulating evidence shows that HMGB1 plays a dual faced role in cardiac injury and remodelling. Cardiomyocytes respond to different pathological injuries in a coordinated multistep process. Basically, three distinct events characterize the process of cardiac injury and subsequent inflammation, as follows: (i) production of inflammatory mediators (mainly cytokines and chemokines) by stressed/damaged cardiomyocytes; (ii) recruitment of inflammatory cells to the damaged heart, leading to cytokine secretion that exacerbates cardiac injury, and (iii) release of anti-inflammatory signals or factors to induce lymphocyte apoptosis or homing and inflammatory resolution, and (iv) occurrence of wound-healing processes and heart remodelling [63].

Cardiomyocytes produce DAMPs such as HMGB1. HMGB1 activates endothelial cells, expresses chemokine receptors, produces inflammatory factors, and induces cardiomyocyte necrosis or necroptosis. Furthermore, HMGB1 promotes the recruitment of inflammatory cells, such as macrophages and neutrophils, to the injured heart by CXCL12/CXCR4. Macrophages are found extensively in all body tissues and exhibit high plasticity and functional heterogeneity. Macrophages participate in host defence against pathogens, foetal and tissue development, metabolism, and wound healing [64]. In this milieu, macrophage differentiation/polarization can be divided into two phenotypes, the classical M1 and alternative M2 phenotypes, which mirror Th1-Th2 polarization and represent two extremes of macrophage activation state changes [65]. The M1 phenotype is closely linked with tissue destruction and inflammation [66]. HMGB1 has been reported to transduce signals by interacting with important receptors, including RAGE and TLR2/4. TLR2/TLR4 and RAGE signalling induce NF-κB and extracellular signal-regulated kinases (Erk)1/2 signalling, which trigger cytokine production [67]. Alternatively, activated M2 macrophages are stimulated by IL-4/13, which restricts inflammatory responses through IL-10 secretion and mediates tissue repair [68]. It was previously described that $CD68^+$ macrophages accumulate during ischaemic heart disease and idiopathic dilated cardiomyopathy and cause the release of M1 macrophage-associated pro-inflammatory factors [69], such as IFN-γ, IL-6, IL-1β, and TNF-α [70]. Moreover, in ageing SAMP8 mice, $CD68^+$ cells accumulate in the heart with the upregulation of HMGB1, IFN-γ, IL-6, IL-1β, TNFα, TNFR1 and COX2 expression [71].

The traditional hypothesis regarding tissue macrophage development was that circulating monocytes differentiate into tissue macrophages. However, recently, tissue resident macrophages might be established prenatally, persist through adulthood, and self-renew by proliferation or by independent or partially dependent input from circulating monocytes [72]. Cardiac resident macrophage renewal is dependent on proliferation and input from circulating monocytes.

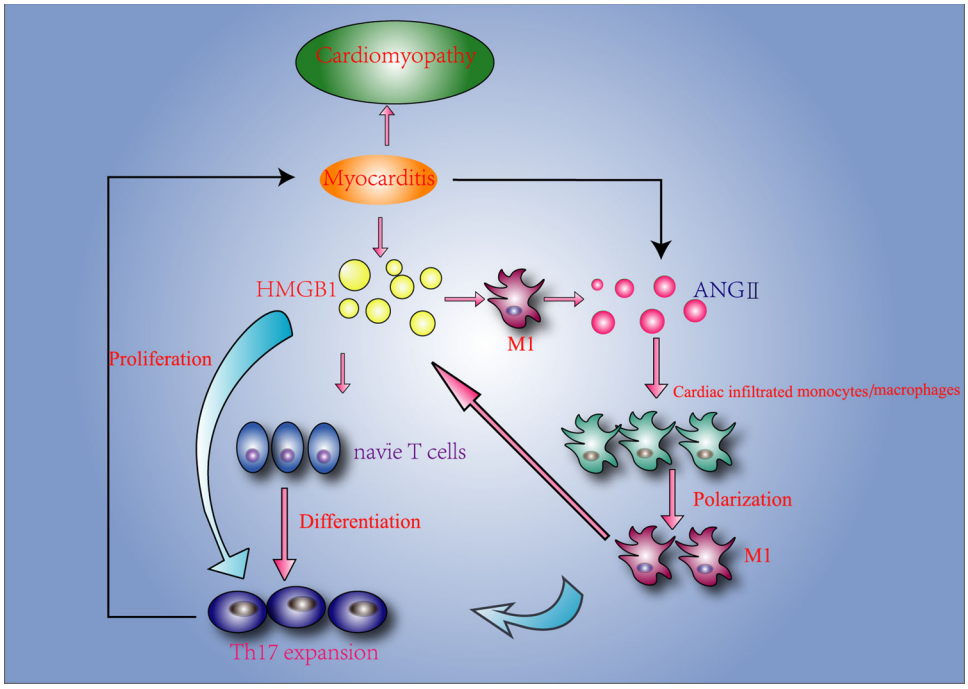

Fig. 4. HMGB1 promotes EAM development by facilitating Th17 expansion or benefiting the polarization of monocytes/macrophages. In the EAM model, HMGB1 and angiotensin II (ANG II) are produced following cardiac injury. On the one hand, HMGB1 directly promotes Th17 cell expansion, and on the other hand, HMGB1 facilitates monocyte/macrophage polarization into the M1 phenotype and then induces a Th17-mediated immune response. Furthermore, ANG II recruits Ly6C$^+$ monocytes/macrophages from the spleen into the heart, and angiotensin II induces polarization of the cells into an M1 phenotype. Additionally, ANG II and HMGB1 can crosstalk and form a positive loop.

Following cardiac injury, cardiac resident macrophages home to peripheral immune organs. HMGB1 and angiotensin II (ANG II) produced by stressed cardiomyocytes or immune cells can recruit Ly6C$^+$ monocytes into the injured heart [73] and reprogram the infiltrated monocytes into M1 macrophages. The reprogrammed M1 macrophages can promote CD4$^+$T cell expansion and promote cardiac injury in experimental autoimmune myocarditis (EAM) (Fig. 4) [74].

CD4$^+$T cells regulate appropriate cellular and humoral immune responses in the progression of many diseases, including myocarditis. We have previously reported that crosstalk between cardiomyocytes and other CD4$^+$ T cells is responsible for the pathogenesis of myocarditis [75]. Endogenous or exogenous HMGB1 is known to play a role in DC activation and CD4$^+$ T cell polarization [76], and after priming, CD4$^+$T cells can differentiate into several major effectors subsets, including Th1, Th2, Th9, Treg and Th17 cells. Emerging evidence has demonstrated that several Th subsets, such as Th1, Th2, Treg, and Th17 cells, but not Th9 cells, are involved in the pathogenesis of myocarditis [77]. Additionally, HMGB1 can directly promote Th17 cell expansion or can indirectly facilitate macrophage reprogramming to M1 phenotype. Th17 cells produce IL-17, recruit neutrophils and accelerate cardiac injury in an EAM model (Fig. 4) [78].

5.2. HMGB1 and efferocytosis, cardiac inflammatory resolution

The removal of apoptotic cells, also called efferocytosis, is an important characteristic of immune responses and is essential for inflammatory resolution. Deficient clearance and impaired efferocytosis are associated with an unfavourable outcome in acute and chronic inflammatory diseases [79]. HMGB1 diminishes phagocytosis of apoptotic neutrophils by macrophages in vivo and in vitro via binding to phosphatidylserine (PS) on the surface of apoptotic neutrophils [80]. Friggeri et al. demonstrated that the interaction of HMGB1 with αvβ3-integrin on the macrophage surface abrogates the binding of milk fat globule EGF factor 8 (MFG-E8) to these structures and thereby affects opsonin activity [81]. Of course, the data also suggest that the HMGB1 C-terminal tail is responsible for the inhibitory effects of HMGB1 on efferocytosis. All the data show that HMGB1 can prolong the inflammatory process by inhibiting efferocytosis of macrophages. Therefore, HMGB1 blockade could significantly ameliorate inflammatory progression.

Although immune activation and persistent inflammation are thought to contribute to the progression of myocarditis, the specific pathological mechanisms and exact cause of immune activation remain unknown. The active inflammatory status during the pathogenesis of myocarditis may cause increased levels of myeloid-derived suppressor cells (MDSCs) that lead to the maintenance of immune homeostasis. MDSCs, a heterogeneous population of cells, play a vital role in the subversion, inhibition, and downregulation of the immune response to cancer, autoimmune diseases, and inflammation-mediated diseases, including myocarditis. Increases in the frequencies and suppressive functions of circulating CD14$^+$HLA-DR$^{-/low}$ MDSCs are found in dilated cardiomyopathy (DCM) patients compared with healthy controls, indicating the participation of MDSCs in the immunomodulatory process of DCM. As a defensive response to pathogens near or within cardiac myocytes, activated monocytes and lymphocytes migrate to the myocardium [82]. The presence of these cells induces the production of inflammatory mediators, which activate MDSCs, drive their accumulation, and strengthen their suppressive activity [83,84]. Zhang et al. hypothesized that MDSCs may participate in the immunomodulatory process through the suppression of uncontrolled T cell activation partially via Arg-1, which further leads to myocardial injury and aggravation of cardiac function, thereby preventing the development of a more severe and fatal immune response in DCM patients [85]. Gr1$^+$CD11b$^+$ MDSCs, especially Ly6C$^+$CD11b$^+$ MDSCs, are upregulated in the EAM mouse model [86]. Given these findings, we hypothesize that the local contexts of inflammatory microenvironments may greatly influence the tissue recruitment, retention, and immunomodulatory capabilities of MDSCs, which subsequently suppress abnormal immune responses and prevent the development of a more severe and possibly fatal immune response in cardiac patients. HMGB1 is likely to activate and drive MDSCs because it induces, chaperones, and/or enhances the activity of several pro-inflammatory molecules that regulate MDSCs [87]. For example, IL-1β drives MDSC accumulation and T cell suppressive activity and is induced by HMGB1 [88]. Complexes of HMGB1 and IL-1β have increased pro-inflammatory activity relative to either molecule alone [89]. Furthermore, HMGB1 from cancer cells could promote M-MDSC differentiation from bone marrow progenitor cells and facilitates conversion of monocytes into MDSC-like

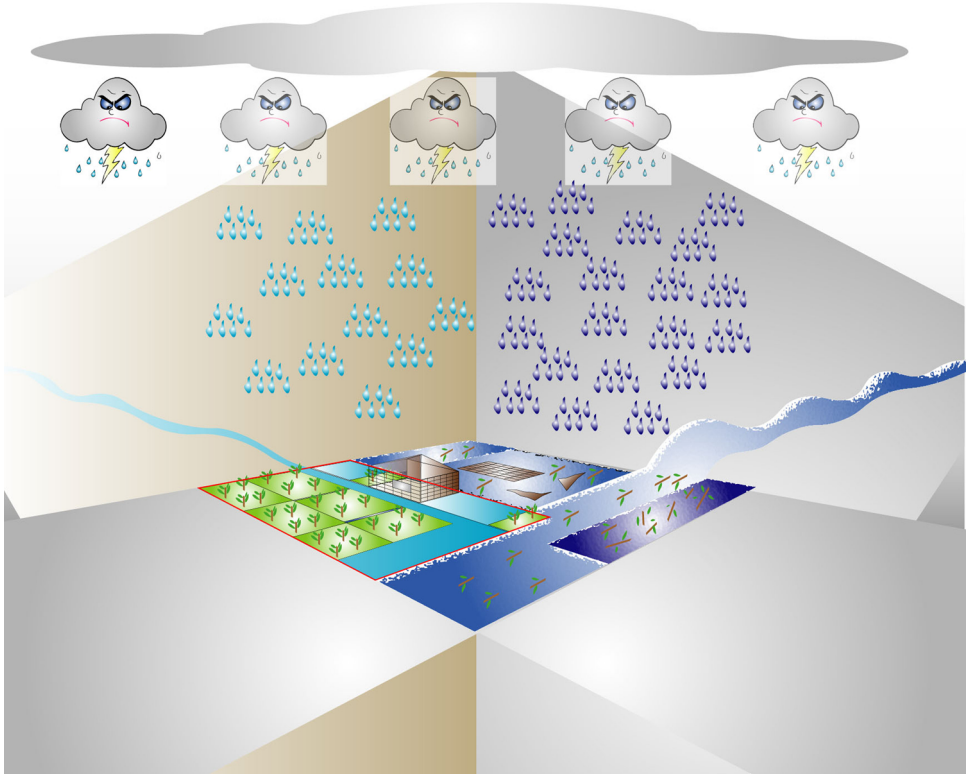

Fig. 5. Is HMGB1 a great scourge or flowing water?

cells [41,87].

However, a novel family of innate immune cells (ILCs) has recently been characterized and found to play an essential role in the initiation, development and resolution of inflammation. ILCs include three subsets, termed group 1, 2 or 3 ILCs, according to the expression of different surface markers, transcription factors and cytokines [90]. ILCs are enriched at barrier surfaces, such as the skin, intestine, and lung, as well as in adipose tissue and some mucosal-associated lymphoid tissues [91–93]. ILCs also exist in the heart under cardiac stress (data unpublished). ILCs benefit the acute inflammatory response or the response against pathogens. Furthermore, ILCs also directly contribute to inflammatory resolution by repairing damaged tissues in the lung, gastrointestinal tract and various lymphoid tissues, which is essential to limit inflammation, prevent against re-infection, and remodel tissues. All-thiol or disulphide HMGB1 could promote ILC3 expansion, and the expanded ILC3 population produced high levels of IL-22 to ameliorate EAM development (data unpublished). Therefore, results regarding the pro-inflammatory or anti-inflammatory roles of HMGB1 following cardiac injury are controversial. One possible explanation is attributed to different isoforms of HMGB1, and the second is associated with the stage of the disease development. Some factors are released during a specific stage of disease development, and the specific factors may form a complex with HMGB1 and play completely different roles. Of course, the controversy may be caused by the different sources of HMGB1 used by different research groups.

5.3. HMGB1 in cardiac fibrosis and cardiac functional remodelling

Cardiac fibrosis is a common pathophysiologic companion of most cardiac diseases and is usually associated with systolic and diastolic dysfunction, arrhythmogenesis and other adverse outcomes [94]. Cardiac fibrosis, which is characterized by over-accumulation of myofibroblasts and deposition of increasing amounts of extracellular matrix (ECM) proteins in the myocardium, is defined as a key component of heart failure [95]. In other words, activated myofibroblasts are effector cells in cardiac fibrosis. Several other cell types, including cardiomyocytes, endothelial cells, pericytes, macrophages, lymphocytes, and mast cells, contribute to the fibrotic process by producing proteases that participate in matrix metabolism through the production of fibrogenic mediators and matrix proteins [94]. The molecular mechanisms underlying cardiac fibrosis are not clear, and the factors contributing to cardiac dysfunction remain to be explored. Recently, HMGB1 is upregulated in the heart tissue and serum, and HMGB1 blockade can ameliorate cardiac fibrosis in EAM; however, it is unknown whether high levels of HMGB1 in EAM can directly lead to cardiac fibrosis. Cardiac endothelial cells, cardiomyocytes and cardiac fibroblasts/myofibroblasts can actively secrete HMGB1, and HMGB1 leads to cardiac fibrosis via autocrine PKCβ activation; HMGB1 blockade could efficiently ameliorate cardiac fibrosis in EAM mice [42,43].

As is well-known, unlike during embryonic development, adult mammalian cardiomyocytes fail to proliferate, replenish or regenerate in the heart following injury, which is a leading cause of heart failure and death worldwide. All adult mammals have limited cardiac regeneration potential; in contrast, some vertebrates, such as the newt and zebrafish, can regenerate their myocardium throughout life [96,97]. However, some data indicate that mammals have cardiac regeneration potential during their adult life, including humans [98,99]. Additionally, the neonatal mouse heart has a regenerative ability immediately after birth [100]. Since the HMGB1 shuttle is considered a key determinant of senescent cells [31–33], whether HMGB1 is associated with cardiac regeneration has been an important question. Recently, all-thiol, not disulphide, HMGB1 orchestrates muscle and liver regeneration via the CXCR4 pathway [10]. The mechanisms of cardiac regeneration among model organisms or neonatal mice are similar. Inflammation, ECM deposition, functional remodelling, and cardiomyocyte proliferation are found in heart regeneration models, but why adult mammals develop extensive scarring instead of undergo regeneration remains a crucial question.

6. Concluding remarks

Many studies have demonstrated that HMGB1 plays different roles in cardiac injury depending on localization, post-translational modifications and receptor binding, and the various mechanisms underlying the activities of HMGB1 have also been described. In conclusion, HMGB1 plays a dual faced role in cardiac injury. HMGB1 can aggravate inflammatory damage, but a timely HMGB1 blockade can effectively ameliorate the progression of cardiac damage. In this regard, HMGB1 is like a flood induced by the pouring rain; the correct guidance can irrigate the field and moisturize the seedlings. Conversely, its action can be like a great scourge, which can destroy a home (Fig. 5). Therefore, we can speculate that HMGB1 is a potential checkpoint for cardiac injury.

7. Remaining questions for the future

However, there are also many questions that need to be addressed, including the following: 1) As a nuclear factor, how does HMGB1 modulate or control cardiomyocyte senescence? Is HMGB1 a checkpoint of cardiomyocyte fate?; 2) As a cytokine, does HMGB1 benefit cardiac regeneration?; 3) Since the resolution of inflammation is an active process, does HMGB initiate the resolution of inflammation following cardiac injury? 4) There is undoubtedly that HMGB1 is a critical effector molecule and plays an important role in cardiac injury, which makes HMGB1 as an attractive biomarker and therapeutic target. The neutralizing anti-HMGB1 antibodies and recombinant A box have been used and shown success in animal models. Next, HMGB1 antagonists will be used for cardiovascular diseases and safety will be an important issue.

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Conflict of interest disclosures

The authors declare no conflict of interest.

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Hongxiang Lu, a candidate Ph.D. of Jiangsu University, focuses on the mechanism of cardiac inflammation injury.

Zhenzhen Zhang received her MD in Pharmacology from Second Military Medical University, China. She is a researcher and focuses on immune regulation of extracted components from traditional Chinese Medicine.

Prince Amoah Barnie obtained his PhD from Jiangsu University. He is originally from Ghana, as a senior lecturer at the Department of Biomedical Sciences, University of Cape coast. Currently, he is a Post-Doctoral Research Fellow at Su's Lab and focuses on molecular and cellular basis of myocarditis.

Zhaoliang Su received his PhD from Jiangsu University, China. He is currently an Executive Director of International Genome Center, Jiangsu University and focuses on the potential mechanisms of cardiac inflammatory injury, inflammatory resolution and cardiac functional remodeling.