Review Article

High mobility group box-1 and cardiovascular diseases

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ABSTRACT

تنتشر مجموعة البروتينات عالية الحركة الأولى (HMGB1) بكثرة وبشكل واسع في النواة والسيتوبلازم لجميع الخلايا. كما تنتقل مجموعة البروتينات عالية الحركة الأولى (HMGB1) من الخلايا النخرية وتنشط وظائف الخلايا وحيدة النواة والخلايا البالعة الكبيرة كمؤشر حرج للالتهاب وتساعد في إصلاح الأنسجة وتجددها وذلك بعد اتحادها مع مستقبلها. أظهرت دراسات عديدة أن مجموعة البروتينات عالية الحركة الأولى (HMGB1) تلعب دوراً جوهرياً في أمراض الأوعية القلبية مثل تصلب الشرايين، وإقفار عضلة القلب، وإصابة إعادة التروية، واعتلال القلب، والإحتشاء العضلي القلبي. في هذه المراجعة، نحن هنا بصدد تسليط الضوء على مجموعة البروتينات عالية الحركة الأولى (HMGB1) وتوضيح العلاقة بينها وبين أمراض الأوعية القلبية.

High mobility group box-1 (HMGB1) is a highly conserved, ubiquitous protein in the nuclei and cytoplasm of almost all cells. After binding to its receptor, HMGB1, which is derived from necrotic cells and activated macrophages/monocytes, functions as a critical mediator of inflammation and promotes tissue repair and regeneration. Many recent studies demonstrated that HMGB1 played a pivotal role in cardiovascular diseases, such as atherosclerosis, myocardial ischemia/reperfusion injury, heart failure, and myocardial infarction. In this review, we focus on HMGB1 and summarize the association of HMGB1 with cardiovascular diseases.

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Owning to the increasing age of the population and improved living standards, cardiovascular disease is the major human disease with a rising incidence and prevalence over recent decades. Accumulating studies have shown that various factors are essential components of the complex pathophysiological process in heart diseases and/or play a crucial role in cardiac repair. To explore the complex disease process and potential therapeutic methods, we describe one such factor, high mobility group box-1 (HMGB1), and its role in the pathogenesis of cardiovascular diseases states.

HMGB1 structure and function. The HMGB1 protein was first termed approximately 30 years ago as a nonhistone chromosomal protein with high electrophoretic mobility.[1] The HMGB1 protein, which is among the most evolutionarily conserved proteins, has 215 amino acids and shares 99% identity in amino acid sequence between rodent and human.[1] The human HMGB1 gene is located on chromosome 13q12 and encodes a protein of 216 amino acids.[2] The structure of HMGB1 comprises 2 domains composed of 80 amino acids referred to as HMG boxes A and B as well as a negatively charged C terminus.[3] More recent findings suggest that the B-box possesses the pro-inflammatory properties of HMGB1 including cytokine release, and the A-box instead competes with HMGB1 for binding sites leading to attenuation of the inflammatory cascade.[4-6] The highly conserved N and C terminal regions of the protein are enriched with basic and acidic amino acid residues. The HMGB1 is located in the nucleus and cytoplasm of most cells and is widely distributed in many organs cells (such as lymphoid tissue, brain, liver, lung, heart, spleen, kidney, and so forth).[7] As a DNA-binding protein, HMGB1 is involved in maintenance of nucleosome structure, regulating gene transcription, and modulating the activity of steroid hormone receptors by interacting with many transcription factors, replication proteins, and steroid

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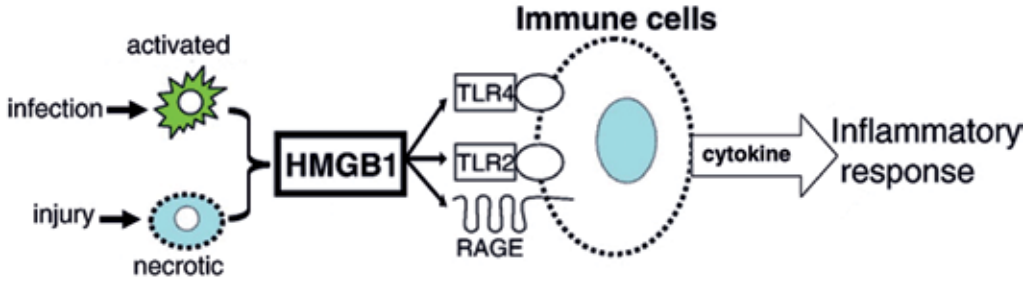

Figure 1 - The HMGB1 induces inflammatory responses. The HMGB1 can be actively secreted via innate immune cells in response to infection or passively released from injured or necrotic cells. Exogenous HMGB1 can enhance the release of pro-inflammatory cytokines and induce harmful inflammatory responses by binding to its receptors (RAGE, TLR2, and TLR4). HMGBI - high mobility group box-1, RAGE - receptors for advanced glycation end products, TLR2 - Toll-like receptor 2, TRL4 - Toll-like receptor 4. Figure reprinted from Yang H, Tracey KJ. Targeting HMGB1 in inflammation. Biochim Biophys Acta 2010; 1799: 149-156, with permission from Elsevier.

receptors.[8] Extracellularly, HMGB1 is released passively by necrotic or damaged cells and secreted actively by immune cells such as monocytes, macrophages, and dendritic cells.[9] Once released into the gap, HMGB1 can transmit the injury signal to neighboring immune cells and thus trigger a rigorous inflammatory response (**Figure 1**).[9] Many studies demonstrated that HMGB1 as a pro-inflammatory cytokine is involved in pathological states, including severe sepsis, tumor metastasis and invasion, pneumonia synovitis, atherosclerosis,[10] vascular restenosis, and arthritis.[11] In addition, HMGB1, also as an injury signal factor, promotes tissue repair and regeneration by activating stem cell migration, proliferation, chemotaxis, as well as participating in an adaptive immune response.[10,12,13]

HMGB1 receptors. The HMGB1 receptors include the receptors for advanced glycation end products (RAGE) and members of the Toll-like family of receptors (TLRs). The RAGE as a multiligand-binding member of the immunoglobulin superfamily are expressed on a variety of cells, and can bind several members of the S100/calgranulin family, the advanced glycation end products (AGEs), HMGB1, β-amyloid peptides, and β-sheet fibers.[14] Following release, HMGB1 binds on the cell-surface RAGE receptors resulting in activation of mitogen-activated protein kinases and transcription factor Nuclear Factor-Kappa B (NF-κ B), which induces production of various pro-inflammatory cytokines.[15,16] In addition to RAGE, TLRs have been demonstrated to be of importance in HMGB1 signaling. The TLRs can recognize both damage-associated molecular patterns and pathogen-associated molecular patterns and are involved in immune response to both infection and injury. The HMGB1 binding of TLR2 and TLR4 results in NF-κ B upregulation and mediates various cellular responses including the movement of chemotactic cells as well as cytokine release.[17,18] Consistently, TLR4-defective (C3H/HeJ) mice are more resistant to HMGB1-mediated ischemic injury,[19] suggesting that TLR4 plays an important role in HMGB1-mediated inflammatory responses.

Table 1 - The main role of HMGB1 in cardiovascular diseases.

Cardiovascular disease	Main role of HMGB1
Atherosclerosis	Promote inflammation and atherogenesis
Myocardial I/R	
Early stage	Promote inflammatory response
Later stage	Induce repair and regeneration of myocardium
Post-MI chronically failing hearts	Reduce the accumulation of inflammatory cells
After MI	
Early stage	Modulate inflammatory response
Later stage	Lead to myocardial repair

HMGB1 - high mobility group box-1, I/R - ischemia/reperfusion, MI - myocardial infarction

HMGB1 and cardiovascular diseases. The increasing prevalence of cardiovascular diseases poses enormous challenges for health care systems worldwide. The inflammatory response is closely correlated with the occurrence and development of cardiovascular diseases. In light of its pro-inflammatory functions as well as restorative effects leading to tissue repair and myocardium regeneration,[9,10,12,13] the role of HMGB1 in cardiovascular diseases has become an attention focus (**Table 1**).

HMGB1 and atherosclerosis. The pathogenesis of atherosclerosis has been researched for more than one century, and it is now considered a chronic inflammatory disease of the arterial system. Vascular inflammation plays a predominant role in the initiation, progression, and the final steps of atherosclerosis. Vascular injury induces accumulation of monocytes, macrophages, and platelets, which can activate and release pro-inflammatory cytokines and chemokines on the vessel wall.[20,21] The HMGB1 abundantly expressed in vascular endothelial cells can be passively released from injured endothelial cells and thus stimulate

neighboring endothelial cells to express various pro-inflammatory cytokines, chemokines, adhesion molecules, and RAGE, which could in turn further increase the release of HMGB1 and other cytokines.[12,22] At the late stage of atherosclerosis, the activated platelets can also release HMGB1,[23] and thus HMGB1 might contribute to the formation of thrombus and progression of atherosclerosis. For instance, HMGB1 levels dramatically increased in atherosclerotic lesions and in patients with coronary artery diseases.[22,24,25] Recently, Inoue et al[26] demonstrated that activated vascular smooth muscle cells were the source of HMGB1 in human advanced atherosclerotic lesions, and HMGB1 could directly stimulate the production of C-reactive protein, which was an important predictor of coronary artery disease,[27] further suggesting that the release of HMGB1 within atherosclerotic plaques may play a predominant role in promoting inflammation and atherogenesis. Considering the important role in atherosclerosis, HMGB1 is likely to be the target in prevention and treatment of atherosclerosis.

HMGB1 and myocardial ischemia/reperfusion injury. Myocardial reperfusion therapy can preserve myocardial viability and function by reversing myocardial ischemia and limiting the infarct size. However, myocardial ischemia/reperfusion (I/R) injury, which is characterized by a significant inflammatory response may result in the reduction of therapeutic benefit and cardiac function recovery time delay.[28,29] In I/R, endogenous HMGB1 is largely released by necrotic tissue and inflammatory cells and the expression levels of RAGE, TLR2, and TLR4 are increased after myocardium injury enables HMGB1 to effectively mediate an inflammatory response and consequently facilitate the progression of ischemic injury.[16-19] Instead of treatment with recombinant HMGB1, treatment of mice with HMGB1 box A and RAGE knockout mice significantly diminished I/R injury, suggesting that HMGB1 plays a major role in the early stage of I/R injury by binding to RAGE, and accelerated myocardial injury.[30] Furthermore, preconditioning with HMGB1 could induce HMGB1 tolerance and reduce myocardial I/R injury as evidenced by significantly diminished infarct size and decreased inflammatory marker levels compared with those in the I/R group.[31] Additionally, myocardial I/R injury leads to a large number of apoptosis and necrosis of cells. As low levels can be beneficial, HMGB1 released from stressed myocardium could also restore cardiac function by the induction of vessel formation and differentiation of myogenic cells in the late stage of I/R injury. Treatment with HMGB1 can increase the new cells in the ischemic region and participate in the regeneration and repair of ischemic myocardium by activating proliferation, and differentiation of hematopoietic stem cells.[32] Certainly, the mechanisms of these restorative functions are mediated by its receptors (RAGE) that mediate the pro-inflammatory properties of the molecule.[33,34]

HMGB1 and heart failure. The HMGB1 is closely related to heart failure. Patients with heart failure with HMGB1 levels higher than 0.5 ng/ml were inclined to induce their cardiac disorders.[35] Recent research by Takahashi and colleagues[36] revealed that HMGB1 administration reduced cardiomyocyte fibrosis and hypertrophy and enhanced global function of post-myocardial infarction (MI) chronically failing hearts, particularly by reducing accumulation of dendritic cells, which can modulate the expression profile of inflammatory cytokines. These findings suggest that HMGB1 plays dual roles in the pathogenesis of heart failure. The contribution of HMGB1 to these potential mechanisms needs to be further explored.

HMGB1 and myocardial infarction. Myocardial infarction is a potentially fatal event and a common cause of death in adults. Many pro-inflammatory factors increased after an acute MI can regulate myocyte survival and induce additional cellular inflammatory responses.[37] Recently, Kohno et al[38] found that increased serum HMGB1 levels were correlated with pump failure, cardiac rupture, and in-hospital cardiac death in patients with MI. Evidence also demonstrated that HMGB1 can modulate an inflammatory response in the early stages after MI, and later lead to myocardial repair.[39] Furthermore, recent studies[32,40] found that HMGB1 can enhance the myocardial regeneration of infarcted areas after acute MI and result in the improvement of cardiac function via activating growth factors, cytokines, and chemokines released by cardiac fibroblasts as well as cardiac C-kit+ cell proliferation and differentiation.

In conclusion, the robust associations between HMGB1 and cardiovascular disease have been demonstrated in this article. As the mechanisms promoting the release of HMGB1, and the signaling pathways it activates, remain to be completely elucidated, evidence that suggests its potential as a therapeutic target/agent in various heart diseases needs to be accumulated. Considering the notable role in inflammation and tissue repair, a therapeutic approach involving the HMGB1-mediated signaling pathway may constitute a new strategy for cardiovascular diseases. Future studies will help to understand the feasibility of such an approach.

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