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HMGB1 and repair: focus on the heart

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ABSTRACT

High-mobility group box 1 (HMGB1) is one of the most abundant proteins in eukaryotes and the best characterized damage-associated molecular pattern (DAMP).
The biological activities of HMGB1 depend on its subcellular location, context and post-translational modifications. Inside the *nucleus*, HMGB1 is engaged in many DNA events such as DNA repair, transcription regulation and genome stability; in the *cytoplasm*, its main function is to regulate the autophagic flux while in the *extracellular environment*, it possesses more complicated functions and it is involved in a large variety of different processes such as inflammation, migration, invasion, proliferation, differentiation and tissue regeneration.
Due to this pleiotropy, the role of HMGB1 has been vastly investigated in various pathological diseases and a large number of studies have explored its function in cardiovascular pathologies. However, in this contest, the precise mechanism of action of HMGB1 and its therapeutic potential are still very controversial since is debated whether HMGB1 is involved in tissue damage or plays a role in tissue repair and regeneration.
The main focus of this review is to provide an overview of the effects of HMGB1 in different ischemic heart diseases and to discuss its functions in these pathological conditions.

Contents

Abbreviations: HMGB1, High mobility group 1; DAMPs, Damage-associated molecular patterns; DNA, Deoxyribonucleic acid; PAMPs, Pathogen-associated molecular patterns; PPRs, Pattern recognition receptors; TLR, Toll-like receptor; RAGE, Advanced glycation end products receptor; NLS, Nuclear localization signal; HDAC, Histone deacetylase; CXCL12, Chemokine (C-X-C motif) ligand 12; CXCR4, C-X-C chemokine receptor type 4; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; MI, Myocardial infarction; I/R, Ischemia/reperfusion; HF, Heart failure; EPCs, Endothelial progenitor cells; HMGB1-tg, Transgenic mice with cardiac-specific overexpression of HMGB; LV, Left ventricle; PRRs, Pattern-recognition receptors; ACE2, Angiotensin-converting enzyme 2; TNF, Tumor necrosis factor; BMC, Bone marrow mononuclear cell; TAC, Transverse aortic constriction; Ca, Calcium; HIF1, Hypoxia inducible factor 1; H/R, Hypoxia/reoxygenation; mAb, Monoclonal antibody; IL, Interleukin; EP, Ethyl pyruvate; PI3K, Phosphatidylinositide 3-kinase; small non-coding RNA molecules, (miRNAs); STEMI, ST-elevation; NSTEMI, Non-ST-elevation; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide.

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1. Introduction

1.1. A short overview on danger signals. Alarmins

The immune-inflammatory system has the key role to protect our body against any threats and to trigger the repair of any established damage. In this response, 4 specific phases can be recognized including a) the detection of noxious agent or of cell damage; b) the alarm signaling in detecting cells and their metabolic/gene response of defense; c) the repair of damaged cells and molecules; d) the morphological and functional remodeling of the involved tissue/organ (Fig. 1).

In 1989 Janeway theorized that the *detection* of infecting pathogens was achieved through the recognition of conserved molecular motifs, named *pathogen-associated molecular patterns* (PAMPs). These motifs were predicted to be present only in pathogens and to bind to germline-encoded receptors, named in turn *pattern recognition receptors* (PRRs), localized on the surface of several types of cells, especially those belonging to the immuno-inflammatory system. This binding produces the defensive response against the intruders and the reparative and regenerative response in the tissue (Janeway Jr., 1989) (Fig. 1).

The above "Stranger Theory", however, could not explain the reason why strong immuno-inflammatory responses are elicited in sterile conditions such as ischemic injuries, trauma, tumors, tissue transplants, autoimmune diseases and many other conditions of cell stress. On the basis of these exceptions, in 1994 Matzinger proposed the "Danger Theory" in which she postulated that the immuno-inflammatory system has evolved to respond not only to infection *per se* but to non-physiological cell death, damage or stress (Matzinger, 1994). She suggested that the triggering of the immuno-inflammatory system depends also on the sensing of *endogenous danger* signals, collectively termed *damage-associated molecular patterns* (DAMPs) or *alarmins*.

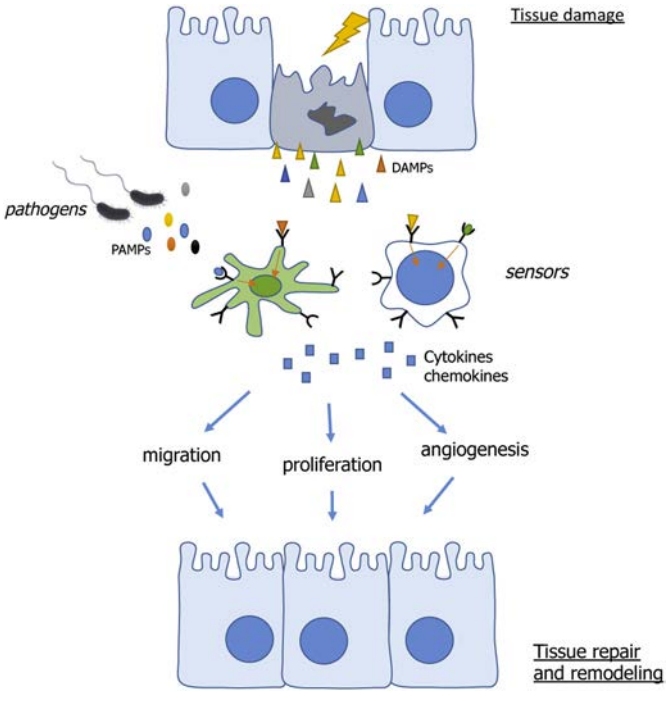

Fig. 1. PAMPs and DAMPs in tissue repair. Pathogen components, termed pathogen-associated molecular patterns (PAMPs), as well as the danger-associated molecular patterns (DAMPs), released by cells under stress condition or following tissue damage, are recognized by receptors present on the surface of sensor cells. These lead to the activation of an inflammatory response and to the release of chemokines and pro-inflammatory cytokines that by inducing proliferation and migration of neighboring cells, and angiogenesis contribute to tissue repair and remodeling.

1.2. The importance of alarmins in human physiopathology

DAMPs or *alarmins* are molecules that act *inside* their cell of origin or *outside* on their close/distant target cells. Physiologically, alarmins are involved in a wide range of intracellular processes including regulation of DNA transcription, calcium homeostasis and cell proliferation and differentiation, while they perform different functions when are outside the cell. Extracellular alarmins can be *passively released* by cells undergoing necrosis, *actively secreted* as acute-phase proteins, *exposed* by cells under stress (Obeid et al., 2007), or can be *proteolytically cleaved* from the extracellular matrix (ECM) following tissue injury (Frey, Schroeder, Manon-Jensen, Iozzo, & Schaefer, 2013; Hsieh, Nastase, Zeng-Brouwers, Iozzo, & Schaefer, 2014; Kono & Rock, 2008). The precise mechanism involved in the active release of DAMPs is still unknown but is thought to be mediated by non-conventional secretory pathways independent of the endoplasmic reticulum and the Golgi apparatus.

Once relocated into the extracellular environment, under conditions of cellular stress or tissue injury, they bind to different types of cellular receptors, mainly PPRs, *alerting* the body about danger, *triggering* inflammation and *promoting* tissue regeneration (Fig. 1). If this signaling, however, is prolonged or intensive, can become harmful for the host and contribute to the pathogenesis or progression of different diseases.

Indeed, high levels of extracellular alarmins have been observed in a wide range of pathological conditions involving cell membrane damage, such as tumors, neurodegenerative diseases, infarction, toxic and infectious diseases. Therefore, extracellular alarmins are constantly and substantially increased in a number of autoimmune, inflammatory, and degenerative disorders such as sepsis, arthritis, brain injury, inflammatory bowel disease, cardiomyopathies and vascular disorders (Chan et al., 2012). Their plasma level indicates, from one side, the severity of the ongoing damage and, from the other side, suggests that alarmins can amplify and sustain the prolonged/inappropriate inflammation that, additionally, can lead to cardiovascular, metabolic, neurodegenerative and malignant disease (Land, 2015). Recently, intracellular alarmins have been shown to localized in microparticles or in exosomes released by virtually any cell under stress in different biological liquids, besides blood plasma, such as cerebrospinal liquor, urine and pleural and peritoneal liquids (Fleshner & Crane, 2017; Maugeri et al., 2018).

In this review, we will summarize these aspects focusing on HMGB1 (High-Mobility Group Box 1), which can be considered the prototype and the best known among the alarmins, and on its role in the major cardiovascular conditions.

2. HMGB1 structure, localization and functions

A typical DAMP or alarmin and one of most studied is the HMGB1, a member of the high mobility group (HMG) protein family. HMG proteins were first isolated from calf thymus nuclei in 1973 by Graham H. Goodwin, Clive Sanders, and Ernest W. Johns while working at Royal Cancer Hospital, Chester Beatty Research Institute in the UK, and named according to their electrophoretic mobility in polyacrylamide gels (Goodwin, Sanders, & Johns, 1973).

HMGB1 is expressed in almost all eukaryotic cells and is highly conserved across all mammalian species with over 99% amino acid identity between rodent and human proteins (Ferrari, Ronfani, Calogero, & Bianchi, 1994; Gariboldi et al., 1995; Sessa & Bianchi, 2007; Wen, Huang, Johnson, & Reeck, 1989). HMGB1 expression is actively inducible in different cells under a number of physiopathological conditions extensively reviewed in (Kang et al., 2014a) and can be modulated by different drugs like aspirin (Mardente et al., 2018), irinotecan (Keyvani-Ghamsari, Rabbani-Chadegani, Sargolzaei, & Shahhoseini, 2017) and oxaliplatin (Liu et al., 2015).

2.1. Structure

The human HMGB1 gene is structured in six exons and encodes a 215 amino acid polypeptide.

It is characterized by a domain organization, consisting of two positively charged homologous DNA-binding domains, named A Box and B Box, and a highly negatively charged C-terminal tail (Bianchi, Falciola, Ferrari, & Lilley, 1992). The A and B boxes, composed of approximately 80 residues each, consist of three α-helices and two loops, arranged in an L-shaped configuration (Read, Cary, Crane-Robinson, Driscoll, & Norman, 1993; Weir et al., 1993), that allow the binding of DNA in a conformation-dependent but sequence-independent manner (Hardman et al., 1995). The BoxA domain contains a heparin binding site (H. Yang et al., 2010) and a proteolytic cleavage site (T. Ito et al., 2008), while the BoxB presents the binding site for the advanced glycation end products receptor (RAGE) and recently it has been shown its ability to bind the extracellular adaptor protein Myeloid Differentiation factor 2 (MD-2) (M. He, Bianchi, Coleman, Tracey, & Al-Abed, 2018) (Fig. 2A). The tail, consisting of 30 glutamic and aspartic acids exclusively (Bianchi et al., 1992), is folded over the protein and regulates DNA binding/bending through intramolecular interaction with the N-terminals of the DNA-binding domains (Stros, 1998; Q. Wang, Zeng, Wang, & Tang, 2007). In addition, the tail is responsible for the maintenance of HMGB1 stability and, consequently, of its proper function (Carballo, Puigdomenech, Tancredi, & Palau, 1984; Cary, Turner, Leung, Mayes, & Crane-Robinson, 1984).

2.2. Post-translational modifications

HMGB1 can undergo several post-translational modifications, including *glycosylation* (Chao, Scovell, & Yan, 1994; Y. H. Kim et al., 2016), *methylation* (Boffa, Sterner, Vidali, & Allfrey, 1979; I. Ito, Fukazawa, & Yoshida, 2007; F. Wu, Zhao, Ding, Wu, & Lu, 2013), ADP-*ribosylation* (Hassa, Haenni, Elser, & Hottiger, 2006; Tanuma, Yagi, & Johnson, 1985), *acetylation* (Bonaldi et al., 2003; Dimov, Alexandrova, & Beltchev, 1990; Sterner, Vidali, & Allfrey, 1979), *phosphorylation* (H. J. Kang et al., 2009; Kimura, Katoh, Sakurada, & Kubo, 1985; Oh et al., 2009; Sun, Johnson, & Allfrey, 1980; Youn & Shin, 2006) and *oxidation* (Hoppe, Talcott, Bhattacharya, Crabb, & Sears, 2006a; Tang et al., 2007).

The *phosphorylation* of serine residues within the nuclear localization signals (NLSs), catalyzed by several protein kinases such as protein kinase C (PKC), calcium/calmodulin-dependent protein kinase type IV (CaMKIV), casein kinase I (CKI), CKII and cyclin-dependent kinase 5 (Cdk5), decreases HMGB1 DNA binding/bending activity (Stemmer, Schwander, Bauw, Fojan, & Grasser, 2002; Ugrinova, Pashev, & Pasheva, 2011; Wisniewski, Schulze, & Sapetto, 1994), and influences HMGB1 nuclear/cytoplasmic distribution and its release (de Abreu da Silva et al., 2011; Oh et al., 2009; Wisniewski et al., 1994; Youn & Shin, 2006; X. Zhang et al., 2008).

The *acetylation*, instead, has been mainly associated to the regulation of HMGB1 cellular localization, albeit, modification of Lys 2 by histone acetyl-transferases CBP (CREB-binding protein) has been reported to significantly enhance HMGB1 affinity to distort DNA structures

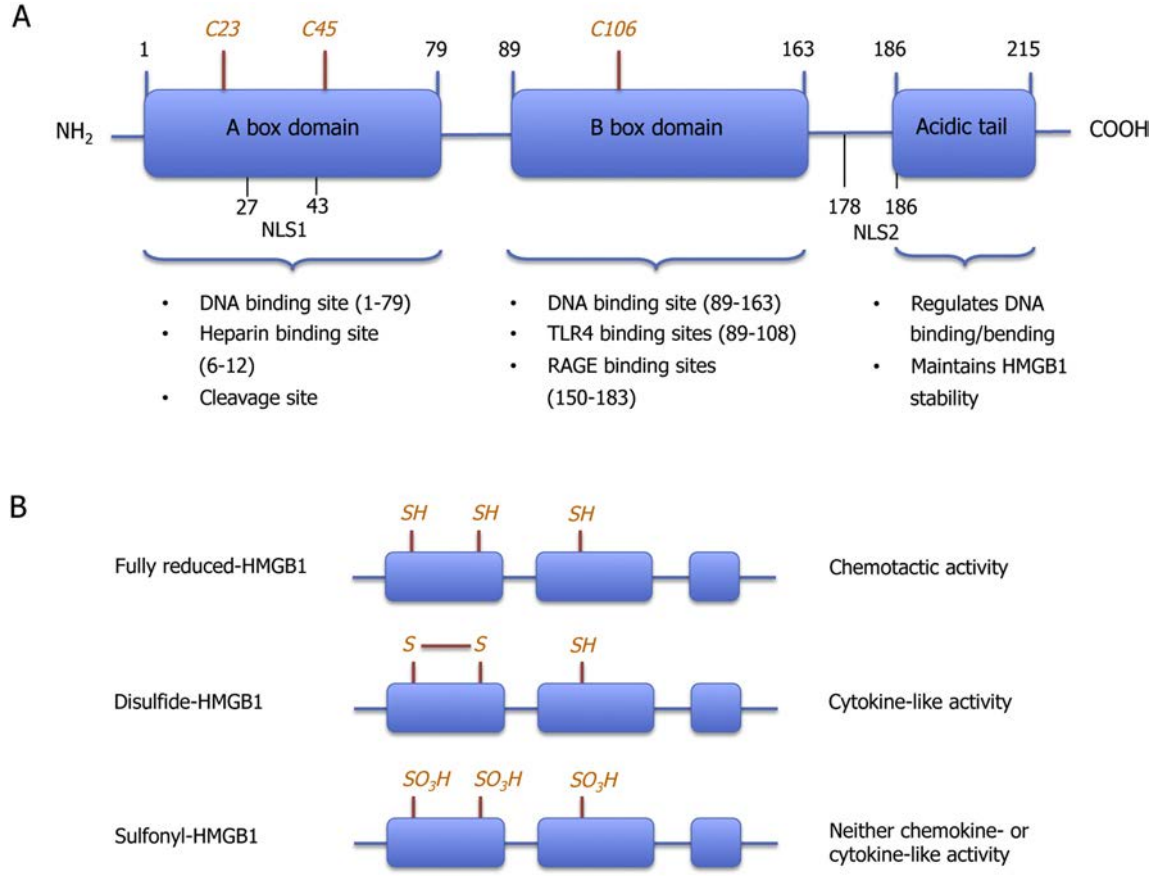

Fig. 2. HMGB1: structural characteristic and redox form (A) HMGB1 is a 215-amino acid protein of 30 kDa organized in three domains: two positively charged domains (A box and B box) and a negatively charged carboxyl terminus (acidic tail). Each domain has peculiar features (B) HMGB1 contains three cystein residues critical for its biological activity. The fully reduced HMGB1 is characterized by all the cystein in the thiol state and exerts chemotactic activity. The partial oxidation of HMGB1 leads to the formation of an intramolecular disulfide bond between the C23 and C45 and defines the disulphide-HMGB1 that acts as a pro-inflammatory cytokine. The further oxidation of all cysteines to sulfonates characterizes the sulfonyl HMGB1 that has neither chemokine- or cytokine-like activity

(Pasheva et al., 2004; Ugrinova, Pasheva, Armengaud, & Pashev, 2001). The acetylation of two main cluster of lysine, localized in the NLSs, by PCAF (Hwang, Lee, Lee, Park, & Jo, 2014; Ong, Lee, Leong, Ng, & Chu, 2012), CBP (Pasheva et al., 2004; C. X. Wu, Sun, Liu, Guo, & Gong, 2012), or p300 (Dhupar et al., 2011), promotes the relocation from the nucleus to the cytoplasm and prevents HMGB1 to reenter the nucleus, a pre-requisite for its extracellular secretion. Indeed, the neutralization of the positive charged NLS by acetylation reduces the binding of HMGB1 to karyopherin-alpha1, the identified nuclear import protein for HMGB1 (Youn & Shin, 2006). On the contrary, the action of histone deacetylase (HDAC) enzymes, in particular HDAC1 (Evankovich et al., 2010), HDAC4 (Evankovich et al., 2010; M. He et al., 2013), HDAC5 (He, Zhou, Zheng, & Jiang, 2013) and SIRT1 (Rabadi et al., 2015; Rickenbacher et al., 2014; Xu, Jiang, Hu, & Fu, 2014), increases HMGB1 nuclear retention, decreasing its release.

Recently, high-resolution proteomic mass spectrometry analyses have revealed that also the *oxidation* plays a major role in defining HMGB1 activity (Venereau et al., 2012; H. Yang et al., 2012). The redox state of the three conserved redox-sensitive cysteines, C23 and C45 (in the Box A) and C106 (in box B) has been linked to the chemokine- or cytokine-like action of HMGB1. When all the cysteines are in the thiol state (fully reduced HMGB1), HMGB1 exerts chemotactic activity, mainly by forming heterocomplexes with the C-X-C motif chemokine 12 (CXCL12) and signaling through the C-X-C chemokine receptor type 4 (CXCR4) receptor. This is the major form observed in the cell (Hoppe, Talcott, Bhattacharya, Crabb, & Sears, 2006b; Venereau et al., 2012). The partial oxidation of HMGB1, with the formation of intramolecular disulfide bond between the C23 and C45 generates a conformation change that stabilizes the molecules (Sahu, Debnath, Takayama, & Iwahara, 2008). This status defines the disulphide-HMGB1 that acts as a pro-inflammatory cytokine. The further oxidation of all cysteines to sulfonates characterizes the sulfonyl HMGB1 that has neither chemokine- or cytokine-like activity (Tang, Billiar, & Lotze, 2012; Venereau et al., 2012; H. Yang, Antoine, Andersson, & Tracey, 2013), but instead provides an anti-inflammatory signal and reduces excessive inflammatory activity (Kazama et al., 2008a) (Fig. 2B). Interestingly, the interplay between the fully reduced and the disulfide HMGB1 isoforms is a reversible process influenced by the redox status of the microenvironment, while the sulfonyl HMGB1 is irreversibly transformed (H. Yang et al., 2013).

Moreover, the oxidation status affects also HMGB1 localization. It has been demonstrated, indeed, that the replacement of C106S or a triple cysteine mutations impaired nuclear localization of HMGB1 (Hoppe et al., 2006b), allowing it to migrate into the cytosol. Conversely, the replacement of Cys23 and/or 45 only with serines did not affect the nuclear distribution of the mutant protein.

2.3. Localization

HMGB1 is constitutively expressed in the nucleus of almost all mammalian cells; however, it can also be found in other cellular compartments and in the extracellular space. In 1979, Michael Bustin was the first to demonstrate the presence of HMGB1 in the cytoplasm of mammalian cells (Bustin & Neihart, 1979). In the subsequent years, many studies have investigated the level and the distribution of HMGB1 between the nucleus and the cytoplasm demonstrating that, in the majority of cell types, HMGB1 continually shuttles between the two cell compartments via passive and active mechanisms, with its equilibrium almost completely shifted towards a nuclear accumulation (Bonaldi et al., 2003). The presence of two nuclear localization signals (NLS), located in the BoxA (aa 28-44) and between the BoxB and the C tail (aa 179–185), respectively, and of two non-classical nuclear exportation signals (NES), present in each of the DNA binding domains, regulates HMGB1 localization (Bonaldi et al., 2003). Following stimulation, indeed, HMGB1 can be rapidly translocated to the cytosol and the rate of this accumulation is determined by post-translational modifications occurring in these two regions (Lu et al., 2014). From the cytoplasm, HMGB1 can be then moved to the membrane or secreted in the extracellular space. However, lacking a classical leader peptide, HMGB1 is not secreted via the Golgi/ER pathway, but it is rather *actively* released via a non-classical vesicle compartment-mediated secretory pathway, that may involve specialized endo-lysosomal vesicles, or it may be secreted associated to exosomes (Gardella et al., 2002; Goetzl, Goetzl, Karliner, Tang, & Pulliam, 2016; H. S. Lee, Jeong, & Lee, 2009; S. Liu et al., 2006; Sheller-Miller, Urrabaz-Garza, Saade, & Menon, 2017; Soop et al., 2013; Valadi et al., 2007). Moreover, HMGB1 can also be found in the extracellular compartment as a consequence of a *passive* release from cells undergoing necrosis (plasma membrane rupture). (Fig. 3) Interestingly, it has been recently demonstrated that HMGB1 can re-enter the cells by binding LPS and leading to its internalization into the lysosomes of macrophages and endothelial cells via the receptor for advanced glycation end-products (RAGE) (Deng et al., 2018).

Finally, HMGB1 can be located on the surface of cells as a membrane-associated protein where it has been shown to mediate neurite outgrowth, platelet activation, erythroid proliferation and maturation, cell differentiation and innate immunity (Parkkinen et al., 1993).

2.4. Receptors and signaling

Most of the extracellular functions of HMGB1 are mediated by its interaction with multiple seemingly unrelated cellular receptors. To date, more than 14 different HMGB1 receptors have been identified and described, including receptor for advanced glycation end-products (RAGE), Toll-like receptors (TLRs; such TLR2, 4, 7 and 9), some proteoglycans (heparan sulfate, phosphacan/PPTP-ζ/β, syndecan and neurocan) (Milev et al., 1998; Salmivirta, Rauvala, Elenius, & Jalkanen, 1992; D. Xu, Young, Song, & Esko, 2011), CD24-Siglec-10 (Chen, Tang, Zheng, & Liu, 2009), CXCR4 (Schiraldi et al., 2012), certain integrins (Mac-1, αVβ3), *N*-methyl-d-aspartate receptor (NMDAR) (Pedrazzi et al., 2012), the triggering receptor expressed on myeloid cells-1 (TREM1) (Wu et al., 2012), CD163 (Yang et al., 2016) and T-cell immunoglobulin domain and mucin domain-3 (TIM-3) (Chiba et al., 2012). Recent studies have demonstrated that the interaction of HMGB1 with TLR4, RAGE and CXCR4 receptors is influenced by its redox status while remains unknown the role of HMGB1 oxidation in regulating the binding and the activation of the other receptors. Moreover, independently of its redox state, HMGB1 can form complexes with other soluble molecules and drammatically enhance responses when compared with the effects of the ligand alone (Campana, Bosurgi, Bianchi, Manfredi, & Rovere-Querini, 2009; Hreggvidsdottir et al., 2012; Sha, Zmijewski, Xu, & Abraham, 2008).

RAGE has been the first HMGB1 receptor to be identified (Hori et al., 1995). It belongs to the immunoglobulin superfamily of transmembrane proteins and contains a V-type domain, which functions for ligand binding, two C-type domains, a transmembrane spinning helix, and a C-terminal cytosolic domain (ctRAGE) which is required for signal transduction (Neeper et al., 1992). RAGE is expressed on a wide variety of cells including endothelial cells, vascular smooth muscle cells, neurons and monocytes/macrophages (reviewed in (Stern, Yan, Yan, & Schmidt, 2002)). Under physiological conditions, its expression is relatively low (Brett et al., 1993), but increases in a ligand-rich environment (Huttunen, Fages, & Rauvala, 1999; J. Li & Schmidt, 1997; Schmidt, Yan, Wautier, & Stern, 1999). The binding of reduced HMGB1 to RAGE leads to the activation of multiple signaling molecules, including ERK 1/2 (Degryse et al., 2001; Ranzato, Patrone, Pedrazzi, & Burlando, 2009), p38 (Qin et al., 2009), stress-activated protein kinase/JNK (F. P. Wang et al., 2013), the Rho family small GTPase CDC42/Rac (Fages, Nolo, Huttunen, Eskelinen, & Rauvala, 2000), Src (Palumbo et al., 2009) and, more importantly, NF-κB, that end up in regulating cell migration, proliferation, differentiation, and adhesion, and inducing the up-regulation of cell surface receptors expression, including TLR4 and RAGE itself (reviewed in (Kang et al., 2014b)). The activation of these signaling

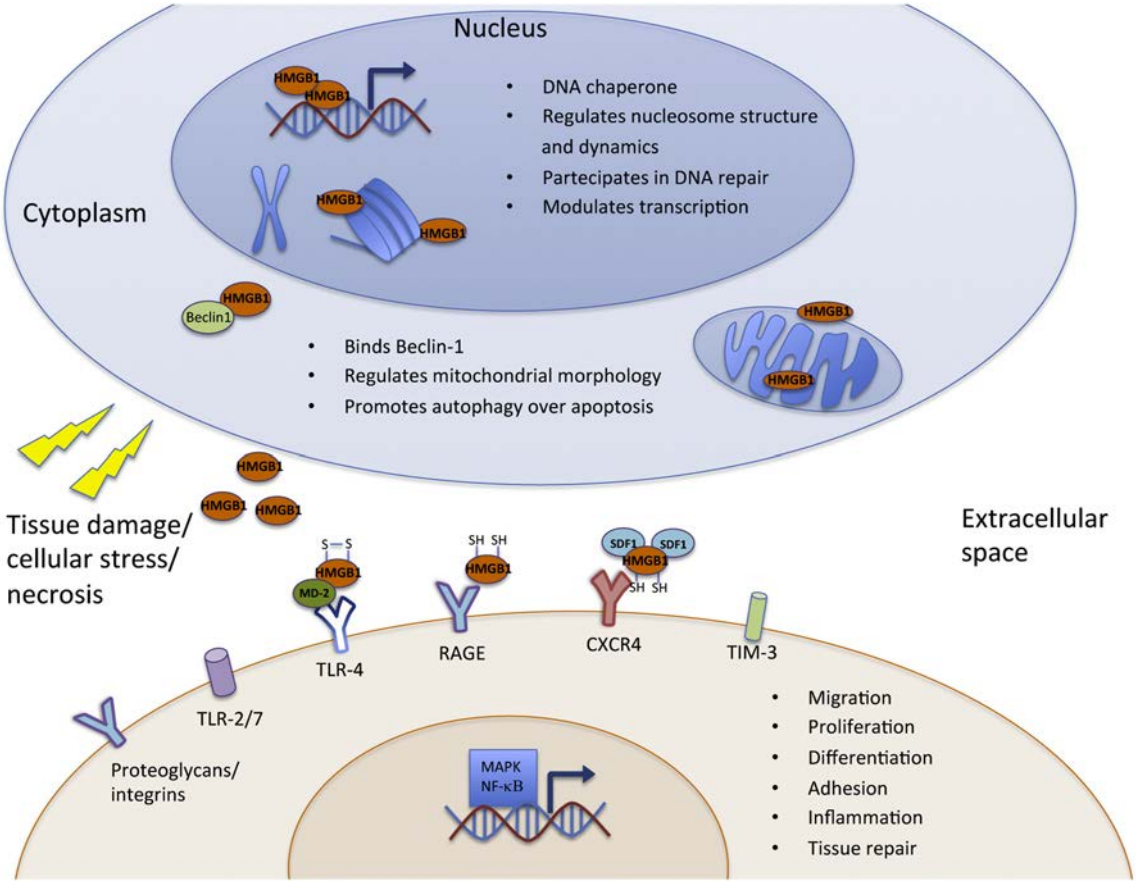

Fig. 3. Main functions of HMGB1 in the different cellular compartments. HMGB1 is a multifunctional protein with various roles in the different cellular compartments. In the nucleus, HMGB1 acts as a DNA chaperone and is involved in transcription, gene regulation and DNA repair. In the cytosol, HMGB1 regulates the autophagic flux and controls mitochondrial dynamics and morphology. Once passively released or actively secreted in the extracellular environment HMGB1 can binds to different receptors, depending on its oxidative status, and leads to the activation of multiple signaling molecules that ends up in regulating cell migration, proliferation, differentiation, and adhesion as wells as inflammation and tissue repair.

pathways has been implicated in several pathological conditions including sepsis (Kokkola et al., 2005; Liliensiek et al., 2004; Lutterloh et al., 2007; H. Yang et al., 2004) as well as cancer (M. K. Fuentes et al., 2007; Sparvero et al., 2009), diabetes, and Alzheimer's disease (S. H. Han, Kim, & Mook-Jung, 2011) and it has been observed in response to hypoxic conditions (Qiu et al., 2008; Tafani et al., 2011). Interestingly, it has been recently demonstrated that in macrophages HMGB1, acting through RAGE, triggers its own dynamin-dependent endocytosis, which in turn initiates a cascade of molecular events leading to cells pyroptosis, that is an highly inflammatory form of programmed cell death (Xu, J., Jiang, Y., et al. (2014); Yang et al., 2016). Moreover, recent studies have shown how the activation of the HMGB1-RAGE axis is important in mediating leukocyte accumulation and in determining the subsequent tissue damage (Jhun et al., 2015; Maugeri et al., 2014; Orlova et al., 2007). In particular, this axis has a major role in early ischemia/reperfusion (I/R) damage, where the prolonged activation of the pro-inflammatory pathways enhanced the myocardial injury (Bangert et al., 2016; K. Liu et al., 2007).

Another receptor involved in mediating the chemotactic activity of HMGB1 is CXCR4. Specifically, reduced HMGB1 can induce the recruitment of inflammatory cells to the site of tissue damage by forming a heterocomplex with the stromal cell-derived factor 1 (SDF1), also known as CXCL12, and then by binding to the CXCR4 receptor (Schiraldi et al., 2012). The HMGB1–CXCL12 complex consists of one molecule of HMGB1 and two molecules of CXCL12, each interacting with one HMG-box domain (Schiraldi et al., 2012). This conformation allows the two molecules of CXCL12 to be presented to a dimer of CXCR4 with the optimal spatial arrangement, thus increasing the effective activity of CXCL12 in inducing cellular responses (Schiraldi et al., 2012). Interestingly, no heterocomplex formation can be detected between disulfide-HMGB1 and CXCL12. The binding of the heterocomplex to CXCR4 homodimers induces the activation of a signaling cascade that involves ERK phosphorylation and $Ca2^{+}$ release from cellular stores (Schiraldi et al., 2012).

The activation of the toll-like receptor 4 (TLR4), instead, is exclusively triggered by the disulfide HMGB1. Recently, through the surface plasmon resonance analysis, it has been shown that also the reduced HMGB1 is able to bind the TLR4 with an equilibrium dissociation constant comparable to the one of to the disulfide, but this last shows a slower dissociation rate, suggesting a more stable binding to the receptor (M. He et al., 2018). Moreover, the activation of TLR4 necessitates an extracellular adaptor, the myeloid differentiation factor 2, which binds specifically to the disulfide HMGB1 to the exclusion of the other isoforms (H. Yang et al., 2015). The binding requires the disulfide Cys23–Cys45 linkage and the Cys106 in its reduced form; indeed, the oxidation of Cys106 prevents HMGB1 from activating TLR4 (H. Yang et al., 2010). This modification might explain the difference between necrotic and apoptotic cells in triggering the inflammatory response. Indeed, necrotic cells release HMGB1 with the reduced form of Cys106 that can initiate inflammation, whereas HMGB1 released during apoptosis has Cys106 in an oxidized state, unable to stimulate TLR4; as a result, the inflammatory response is not induced (Antoine, Williams, Kipar, Laverty, & Park, 2010; Kazama et al., 2008b). Moreover, the activation of TLR4 induced by HMGB1 is dependent on the co-receptor CD14 (S. Kim et al., 2013). Once activated, TLR4 leads to the nuclear translocation of NF-κB, which upregulates the expression of cytokines and other inflammatory mediators, through both the myeloid differentiation primary-response protein 88 (MyD88) and the TIR-domain-containing adapter-inducing

interferon-γ (TRIF)- dependent pathways (Ding et al., 2012a; Zhao, Perez, Lu, George, & Ma, 2014). In the heart, the TLR4-HMGB1 axis has been reported to play an important role in mediating inflammatory and injurious responses associated with heart diseases including myocardial infarction (H. S. Ding et al., 2012a; H. S. Ding et al., 2013; Kaczorowski et al., 2009). In particular, it has been shown that the activation of this axis contributes to the apoptotic death of cardiomyocytes (H. S. Ding et al., 2013; H. Zhu et al., 2013).

2.5. Function

The biological activity of HMGB1 depends on its location, context and post-translational modifications (Fig. 3). In the *nucleus* HMGB1 acts as a DNA chaperone, characterized by DNA binding and bending activities, and regulates several key DNA events. HMGB1 binds to DNA with structure-specificity but not sequence-specificity (Yu, Li, Goodwin, & Johns, 1977). In particular, HMGB1 can bind with relative high affinity to non-canonical or damaged DNA structure, like, among others, H-DNA (Jain, Akanchha, & Rajeswari, 2005), single-stranded DNA (Bidney & Reeck, 1978), semicatened DNA loops (Gaillard & Strauss, 2000), four-way DNA (Bianchi, Beltrame, & Paonessa, 1989; Gaillard & Strauss, 1994; Grasser et al., 1998; Hill & Reeves, 1997; Stros & Muselikova, 2000; Teo et al., 1995) and cisplatin-modified DNA (Stros, 2001). Reduced HMGB1 has a higher affinity for these structures compared to the disulfide form and effectively competes with H1 for binding the four-way DNA junctions (Park & Lippard, 2011; Polanska, Pospisilova, & Stros, 2014; Varga-Weisz, van Holde, & Zlatanova, 1994). Upon binding DNA, HMGB1 can bend the nucleic acid changing its conformation and contributing to several DNA processes. The HMGB1 bending activity was initially reported in 1993 by two separate research groups (Paull, Haykinson, & Johnson, 1993; Pil, Chow, & Lippard, 1993). The model for a basic DNA binding/bending model involves the intercalation of bulky hydrophobic amino acid residues of the HMG-boxes between successive base-pairs within the DNA minor groove, accompanied by partial unwinding, widening of the minor groove, and bending towards the major groove (reviewed in (Thomas, 2001)). Moreover, HMGB1 is involved in the regulation of nucleosome structure and dynamics, as well as in the control of their number and location (Celona et al., 2011; Krynetskaia, Xie, Vucetic, Obradovic, & Krynetskiy, 2008). By binding to the nucleosomes, HMGB1 promotes their sliding and relaxes their structure, making the chromatin more accessible (Travers, 2003). The binding/bending activity of HMGB1, as well as the interaction with the nucleosomes, is a prerequisite for the regulation of gene transcription (S. J. He et al., 2017; Singh & Dixon, 1990) and DNA repair (Lange, Mitchell, & Vasquez, 2008; Lange & Vasquez, 2009).

In addition, in the nucleus HMGB1 is involved in the modulation of DNA replication (Alexandrova, Marekov, & Beltchev, 1984) and in the V(D)J recombination (Agrawal & Schatz, 1997), it regulates telomerase activity and participates in telomeres maintenance (Ke et al., 2015; Polanska, Dobsakova, Dvorackova, Fajkus, & Stros, 2012; Qiang et al., 2014). Further, by inducing the expression of heat shock protein β-1, that allows membrane dynamic trafficking, it plays an important role in the nucleus during autophagy and mitophagy (Tang, Kang, Livesey, & Zeh, H. J.,3rd, & Lotze, M. T., 2011).

In the *cytoplasm,* HMGB1 is present, under normal condition, at low level and in the fully reduced form. The main function of HMGB1 in this cellular compartment is to regulate the autophagic flux. In particular, it has been demonstrated that HMGB1 is a critical pro-autophagic protein that enhances cell survival and limits programmed apoptotic cell death. The disulfide HMGB1 competes with Bcl-2 for binding Beclin-1, which in turn induces autophagy and the degradation of damaged organelles and unused proteins (Tang, Loze, Zeh, & Kang, 2010). The interaction between HMGB1 and Beclin-1 is positively regulated by ULK1 (J. Huang et al., 2012), MAPK (Tang et al., 2010), and NAC (Cheng et al., 2013), but negatively regulated by p53 (Livesey et al., 2012) and synuclein (Song et al., 2014). During inflammation, HMGB1 protects Beclin-1 and ATG5 from calpain-mediated cleavage, decreasing cell death and mitigating in this way the damage of inflammation-associated injury through the regulation of the switch between autophagy and apoptosis (Zhu, X., Messer, J. S., et al. (2015)). HMGB1 induces autophagy also by upregulating the expression of the discoidin domain receptor 1 and downregulating the phosphorylation of mTOR (Ouyang et al., 2016).

The first suggestion for a role of HMGB1 at the plasma membrane level came from the study of Merenmies, Pihlaskari, Laitinen, Wartiovaara, & Rauvala, 1991 where they suggested that HMGB1 was localized in the filopodia of neuroblastoma cells and had a regulatory role in neurite outgrowth (Merenmies et al., 1991). Later studies demonstrated how HMGB1 promotes the generation of surface-bound plasmin, and is involved in cells adhesion and invasion (Parkkinen et al., 1993; Parkkinen & Rauvala, 1991) and how contributes to erythroid maturation (Hanspal & Hanspal, 1994) and in murine erythroleukemia (MEL) cell differentiation (Passalacqua et al., 1997). More recently, it has been showed that HMGB1 is present on cell surface membranes involved in the innate immunity and in platelet activation (E. Fuentes, Rojas, & Palomo, 2014; Maugeri et al., 2012).

In the *extracellular environment* HMGB1 has been found in plasma (soluble and microvesicular/exosomal fraction) (Coleman Jr, Maile, Jones, Cairns, & Crews, 2018; H. Wang et al., 1999), in cerebrospinal fluids (CFS) (Qiu et al., 2008), in pleural and peritoneal liquid (Winter, Meyer, Richter, Krisponeit, & Bullerdiek, 2009) and urine (Oyama et al., 2010). Here HMGB1 performs multiple functions, which results from its forms (e.g., reduced or oxidized, dimer or multimer), its concentration and its interaction with other molecules and receptors. In this compartment, HMGB1 is involved in a vast variety of different processes such as inflammation, migration, invasion, proliferation, differentiation and tissue regeneration. The first evidence of the involvement of HMGB1 in the inflammatory process came from the study of Wang and colleagues that demonstrated how HMGB1 is a late mediator of sepsis (H. Wang et al., 1999). Following studies showed that HMGB1 could bind multiple receptors and stimulate different immune cells to produce a variety of inflammatory-related proteins, such as cytokines, chemokines, adhesion molecules and tissue factors through the activation of several pathways (reviewed in (R. Kang et al., 2014a)). In particular, it has been recently observed that the redox status of HMGB1 determines its role and activity in inflammation and other biological outcomes (Venereau et al., 2012). Indeed, HMGB1 ability to recruit inflammatory cells, like neutrophils and monocytes to the sites of inflammation requires all its three cysteines in a fully reduced status while its cytokine-inducing activity involves a disulfide linkage between C23 and C45.

High level of *circulating* HMGB1 has been found in various diseases since the upregulation of this molecule is frequently associated with their pathogenesis. In the last years, therefore, the use of HMGB1 as possible clinical biomarker has been extensively investigated. Its possible use has been evaluated in autoimmune and inflammatory diseases such as Systemic Lupus Erythematosus (Abdulahad et al., 2012; Koutsonikoli et al., 2017), antineutrophilic cytoplasmatic antibody (ANCA)- associated vasculitis (de Souza et al., 2013) and juvenile idiopathic arthritis (Bobek, Grcevic, Kovacic, Lukic, & Jelusic, 2014; Schierbeck et al., 2013). Fecal HMGB1 has been proposed as biomarker of intestinal mucosal inflammation in patients with inflammatory bowel disease (Palone et al., 2016; Vitali et al., 2011), whereas serum HMGB1 could represent a valuable diagnostic marker in patients with acute appendicitis (Albayrak et al., 2011; Soreide, 2011; Wu et al., 2012). Serum HMGB1 is also an informative biomarker in different models of trauma and in critical illness (Yagmur et al., 2018). Moreover HMGB1 increases in CSF associated with neuronal death in subarachnoid hemorrhage (Tian et al., 2017; K. C. Wang et al., 2017); in several neurological diseases, including cranial hypertension (Walker et al., 2017), Rassmusen's encephalitis (Luan, Gao, Zhai, Chen, & Li, 2016),

multiple sclerosis (Andersson et al., 2008), and in HIV-associated neurological disorders (Gougeon et al., 2017).

In different type of cancer, including gastric cancer, bladder cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, prostate cancer, nasopharyngeal carcinoma, head and neck squamous cell carcinoma, esophageal cancer, malignant pleural mesothelioma, and cervical carcinoma HMGB1 levels have been found to correlate positively with tumor size, stage and outcome (T. Wu et al., 2016). Interestingly the potential clinical value of HMGB1 and RAGE in assessing the severity and prognosis of patients with heart failure (HF) has been also evaluated (Marsh, Nguyen, Parker, & Agrawal, 2017). By performing a prospective analysis based on the data of 11 different studies from 2008 to 2015, Marsh et al. found a positive correlation between the level of HMGB1, RAGE and sRAGE and the worsening HF conditions and increasing New York Heart Associational (NYHA) functional class. Moreover, level of serum HMGB1 was recently positively associated with cardiovascular risk (J. S. Wang et al., 2018; Yamada, Yakabe, Ishii, Imaizumi, & Maruyama, 2006). Importantly, different isoforms of HMGB1 could give additional information on the type or stage of the disease. Antoine and colleagues were the first to show the expression of different isoforms in the different stages in a model of drug-induced liver injury (Antoine et al., 2013). Acetylated HMGB1 has been demonstrated to be a valuable biomarker of acute liver injury (Woolbright et al., 2015). Persistently high level of disulfide HMGB1 has been associated with the likelihood of subsequent seizures (Ravizza et al., 2017; Walker et al., 2017). Concerning cancer, hyper-acetylated HMGB1 has been suggested as a sensitive and specific biomarker to differentiate malignant mesothelioma (MM) patients from asbestos-exposed individuals and from healthy unexposed controls (Napolitano et al., 2016).

3. HMGB1 and heart disease: marker of myocardial damage; IRR trigger and actor

The role of HMGB1 in cardiovascular diseases is very controversial since several studies indicate that it is involved in tissue damage while other studies suggest that it plays a role in tissue repair and regeneration (Fig. 4–6). The main aim of this review is to provide an overview of HMGB1 effects in animal models of permanent ischemia, ischemia/reperfusion (I/R) injury and post-MI HF (Table 1). Further, recent findings on the role of HMGB1 as a biomarker in patients with coronary artery diseases will be discussed (Table 2).

3.1. HMGB1 permanent ischemia and ischemia and reperfusion

3.1.1. HMGB1 and permanent ischemia

Myocardial infarction (MI) triggers a potent inflammatory-reparative response (reviewed in (Frangogiannis, 2015)). Its pathogenesis includes several steps: a) MI induces the necrosis of cardiomyocytes with the following passive release of endogenous DAMPs; b) as described above, alarmins activate the innate immune response, i.e. resident macrophages and leukocytes or cells recruited from the circulation (Ghigo, Franco, Morello, & Hirsch, 2014; Prabhu & Frangogiannis, 2016); c) after binding to their receptor, DAMPs activate NF-κB (or similar transcription factors), leading to the expression of genes encoding inducible enzymes, cytokines and growth factors involved in the protection and repair of the injured tissue (Gordon, Shaw, & Kirshenbaum, 2011). Therefore, the activation of the inflammatory phase, observed following MI, is necessary to eliminate necrotic debris and to initiate the reparative process. In particular, it promotes a rapid healing response that may protect the heart at the expense of preserving structure and function.

Importantly, it has been recently demonstrated that the activation of the inflammatory-reparative response following cardiac injury can also promote myocardial regeneration. Accordingly, the receptors for DAMPs, firstly identified in tissue resident leukocytes (Bianchi, 2007; Iwasaki & Medzhitov, 2004) and later described in many other cells and tissues, under stress conditions, can be induced and expressed *de novo* in resident or recruited stem cells and pluripotent undifferentiated progenitors from many tissues (Ryan, Nissim, & Winyard, 2014; Tafani et al., 2011).

Nevertheless, if the inflammatory response is prolonged or excessive, it might aggravate ischemic damage leading to adverse remodeling and congestive HF (Frangogiannis, 2014). Therefore, an effective

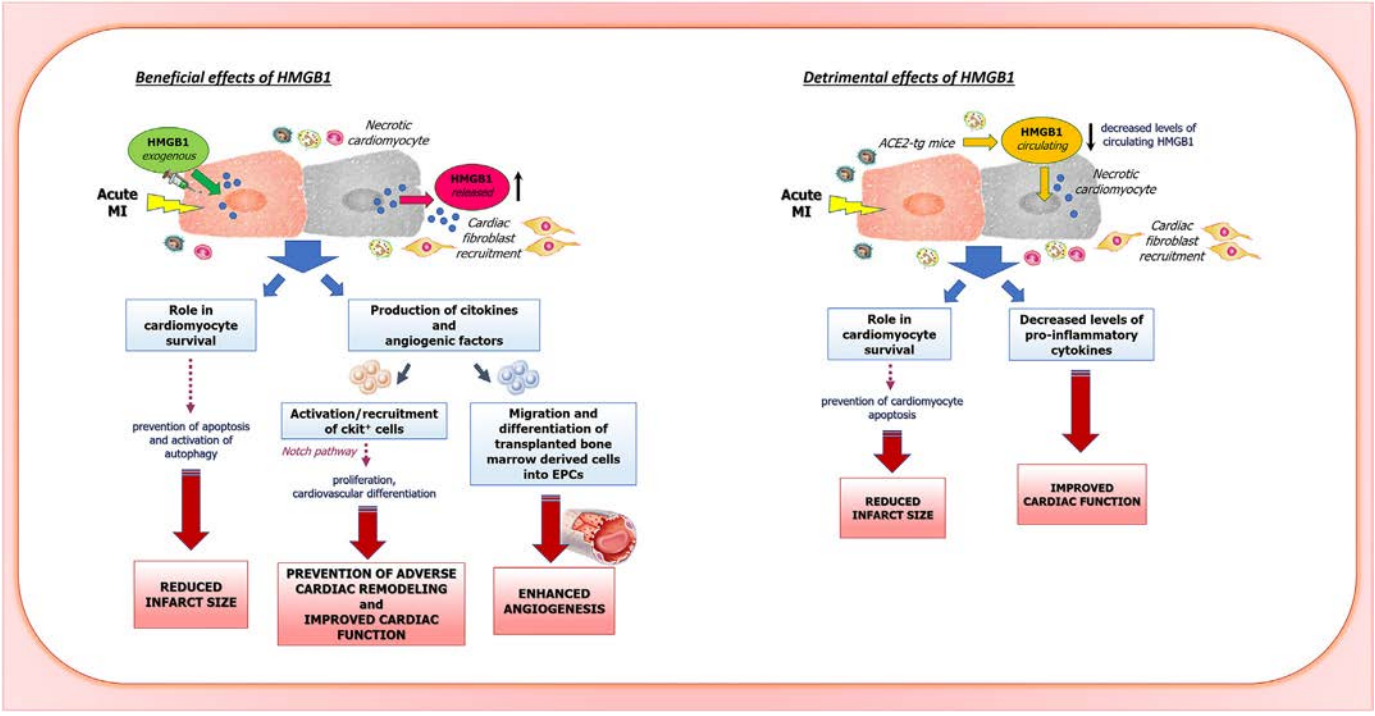

Fig. 4. HMGB1 in permanent ischemia. Schematical representation of the beneficial and detrimental effects of HMGB1 in the experimental *in vivo* model of acute myocardial infarction (MI) induced by permanent coronary ligation.

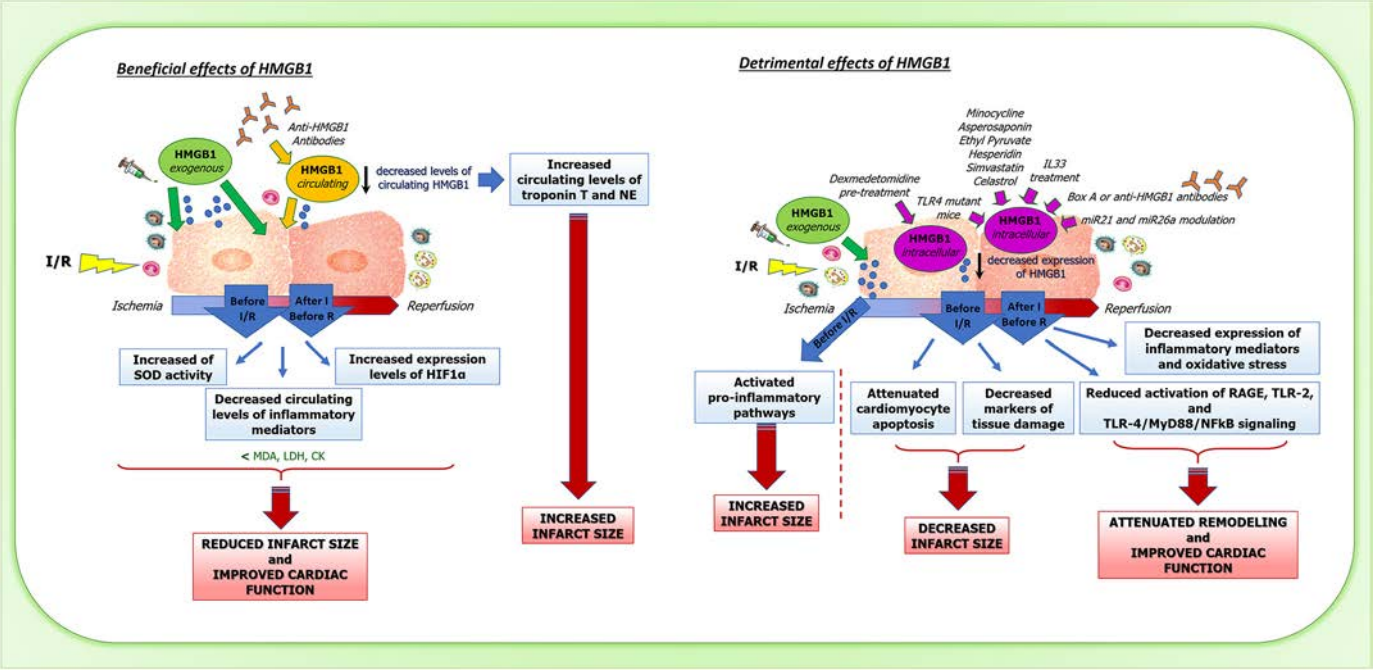

Fig. 5. HMGB1 in ischemia and reperfusion injury. Schematical representation of the beneficial and detrimental effects of HMGB1 in the experimental *in vivo* model of cardiac ischemia/reperfusion (I/R) injury.

therapy should not interfere with the activation of the inflammatory pathway but rather determine its timely restrain and resolution.

In this context, cytokines and other inflammatory mediators, as HMGB1, may represent important regulators of cardiac repair if they activate transient and self-limited inflammation.

3.1.1.1. HMGB1 and cardiac ckit$^+$ cells. In 2005, our laboratory first reported that exogenous HMGB1, injected into the mouse heart, immediately after MI and before the release of endogenous HMGB1, induced a significant improvement in cardiac function and partially prevented left ventricular (LV) remodeling by triggering regeneration (Limana et al., 2005). We showed that the regenerative process involved the proliferation and differentiation of resident ckit$^+$ cells positive for the HMGB1 receptor RAGE, rather than the mobilization of bone marrow-derived ckit$^+$ stem cells, thus suggesting a cardiac origin of newly formed cells in infarcted treated hearts. The contribution of these cells to cardiac regeneration is highly debated, indeed, and the nature of this controversy has been carefully addressed in two recent reports by

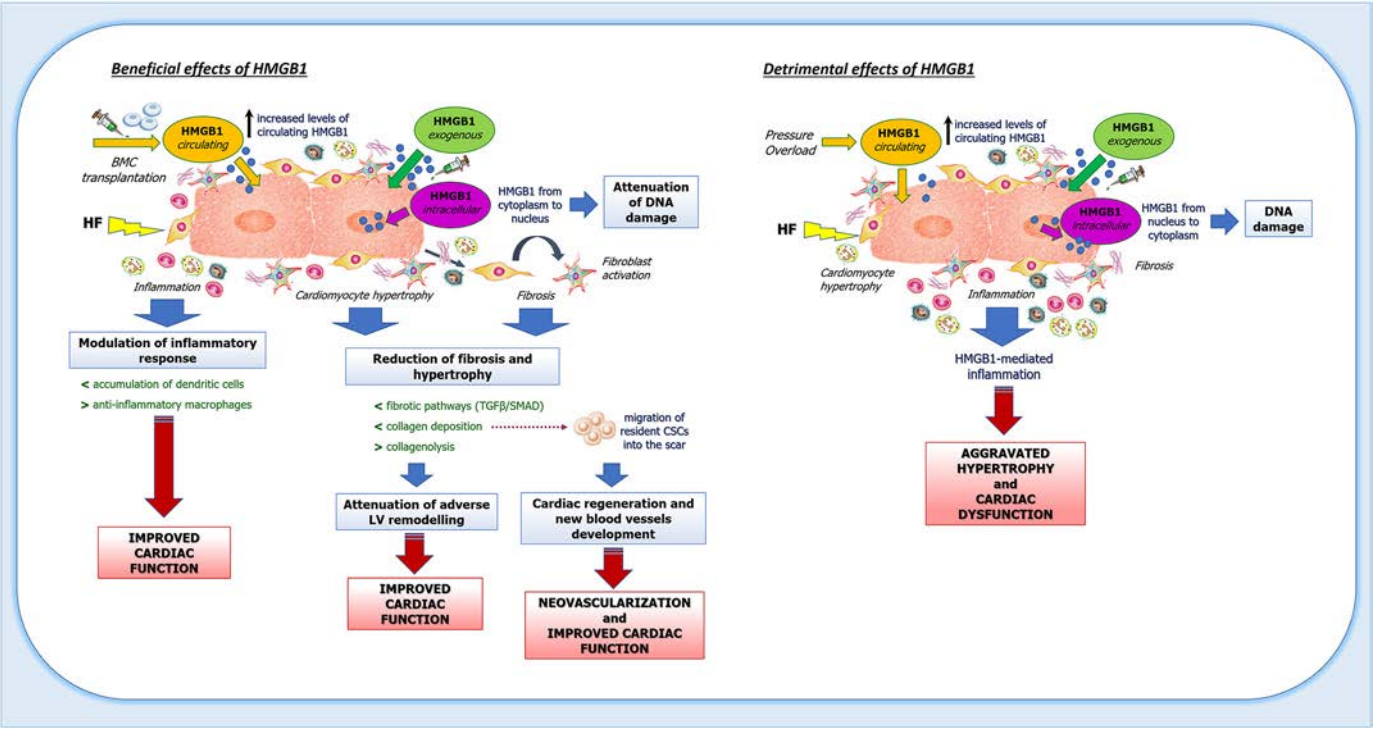

Fig. 6. HMGB1 in heart failure. Schematical representation of the beneficial and detrimental effects of HMGB1 in the experimental *in vivo* model of heart failure (HF).

Table 1
HMGB1 effects in animal models of acute MI, HF and I/R. CK, creatine Kinase; LDH, lactate dehydrogenase; MDA, malondialdehyde; SOD, superoxide dismutase; NE, norephinephrine; Myd88, Myeloid differentiation factor.

Species	Experimental mode	HMGB1	HMGB1-mediated effects	Ref
Mouse	Acute MI	-Exogenous HMGB1 200ng/mouse -Intramyocardial injection -Treatment post-MI	-Cardiac regeneration mediated by ckit$^+$ cells -Prevented cardiac remodeling and improved cardiac function	(Limana et al., 2005)
HMGB1-tg mice	Acute MI	-Endogenous (extracellular) HMGB1 <40ng/ug protein	-Increased circulating levels of HMGB1 -Enhanced angiogenesis -Prevented cardiac remodeling and improved survival and cardiac function	(Kitahara et al., 2008)
HMGB1-tg mice	Acute MI	-Endogenous (extracellular) HMGB1 <40ng/ug protein	-Increased circulating levels of HMGB1 -Enhanced angiogenesis by migration and differentiation of transplanted bone marrow derived cells into EPCs -Reduced infarct size	(Nakamura et al., 2015)
Rat	Acute MI	-Anti-HMGB1 antibody (10mg/Kg/day) -Subcutaneous injection for 7 days -Treatment post-MI	-Deteriorated LV remodeling and cardiac function	(Kohno et al., 2009)
Rat	Acute MI	-Exogenous HMGB1 200ng/rat -Intramyocardial injection -Treatment post-MI	-Activated Wnt b catenin signaling pathway -Improved cardiac function	(Zhou et al., 2012)
Mouse	Acute MI	-Exogenous HMGB1 200ng/mouse -Intramyocardial injection -Treatment post-MI	-Involvement of Notch 1 signaling in HMGB1-mediated proliferation and differentiation of ckit$^+$ cells	(Limana et al., 2013)
Mouse	Acute MI	-Exogenous HMGB1 200ng/mouse -Intramyocardial injection -Treatment post-MI	-Induced autophagy and attenuated apoptosis of cardiomyocytes -Improved cardiac function	(Foglio et al., 2016)
ACE2-tg mice	Acute MI	-Endogenous (extracellular) HMGB1	-Decreased infarct size -Attenuated cardiomyocyte apoptosis -Decreased circulating levels of HMGB1 -Decreased levels of pro-inflammatory cytokines -Improved cardiac function	(Qi et al., 2016)
Rat	Acute MI	-Endogenous (intracellular) HMGB1	-Induced necroptosis by Ad-HGF administration -Increased HMGB1 protein levels -Increased ckit$^+$ cell proliferation and differentiation -Enhanced angiogenesis and cardiac function	(Liu et al., 2016)
WT mice and RAGE -/- mice	I/R (30min I/48h R)	-Exogenous HMGB1 10ug/mouse -Intraperitoneal injection -Treatment before I/R	-Increased infarct size -Activated pro-inflammatory pathways -Involvement of HMGB1-RAGE interactions in cardiac I/R injury.	(Andrassy et al., 2008)
WT mice and RAGE -/- mice	I/R after type I diabetes induction (30min I/4weeks R)	-Exogenous BoxA 400ug/mouse -Intraperitoneal injection -Treatment before I/R	-Attenuated remodeling -Decreased markers of tissue damage -Involvement of HMGB1-RAGE interactions in cardiac I/R injury.	(Volz et al., 2010)
Rat	I/R (30min I/4h R)	-Exogenous HMGB1 200ug/Kg -Intraperitoneal injection -Treatment before I/R	-Decreased infarct size -Decreased levels of CK and LDH -Decreased circulating levels of inflammatory mediators	(Hu, Jiang, et al., 2010)
Rat	I/R (30min I/3h R)	-Exogenous HMGB1 50,100,200ng/Kg -Intravenous injection -Treatment before I/R	-Decreased circulating levels of inflammatory mediators -Decreased levels of MDA -Increased of SOD activity	(D. Y. Zhang et al., 2015)
Rat	I/R (30min I/1h R)	-Exogenous anti-HMGB1mAb -Intravenous injection -Treatment post I and just before R	-Increased infarct size -No differences in cardiac functions -Increased circulating levels of troponin T and NE	(Oozawa et al., 2008)
Rat	I/R *ex vivo* (25min I/1h R)	-Exogenous HMGB1 200ng/ml and 1ug/ml -Intracoronary infusion -Treatment post I and just before R	-Decreased levels of inflammatory mediators -Decreased infarct size -Improved cardiac function only after treatment with 200ng HMGB1	(Abarbanell et al., 2011)
Rat	I/R 30min I/24h R	-Endogenous (intracellular) HMGB1	-Decreased serum levels of HMGB1 following glycyrrhizin treatment -Decreased levels of inflammatory markers -Decreased myocardial apoptosis -Decreased JNK activity	(Zhai et al., 2012)
Rat	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of HMGB1 following minocycline treatment -Decreased levels of LDH, CK and MDA -Increased levels of SOD -Decreased apoptotic index and infarct size	(Hu, Zhou, et al., 2010)
Rat	I/R 30min I/24h R	-Endogenous (intracellular) HMGB1	-Decreased expression of HMGB1 following asperosaponin X treatment	(Jiang et al., 2012)

Table 1 (*continued*)

Species	Experimental mode	HMGB1	HMGB1-mediated effects	Ref
			-Reduced cytotoxicity, NFkB activation and infarct size and ameliorated cardiac function	
Rat	I/R 30min I/48h R	-Endogenous (intracellular) HMGB1	-Decreased expression of HMGB1 following ethyl pyruvate treatment -Decreased expression levels of inflammatory mediators -Reduced cardiac dysfunction	(Lin, Chen, Li, & Fang, 2015)
Rat	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	Under normoglycemia and hyperglycemia conditions: Decreased expression of HMGB1 following ethyl pyruvate treatment -Decreased mRNA levels of inflammatory mediators -Decreased cardiac apoptosis and infarct size -Reduced HMGB1, RAGE, TLR-2 and TLR-4, and NF-κB phosphorylation	(Soh et al., 2018)
Rat	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of HMGB1 following hesperidin treatment -Decreased inflammatory response and oxidative stress -Attenuated cardiomyocyte apoptosis	(Li et al., 2016)
Rat	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of cardiac HMGB1 following simvastatin treatment -Decreased inflammatory response -Decreased infarct size	(Q. F. Han et al., 2015)
Rat	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of HMGB1 following celastrol treatment -Decreased inflammatory response and oxidative stress -Decreased infarct size and cardiomyocyte apoptosis	(Tong et al., 2018)
Rat	I/R 30min I/4h R	- Exogenous HMGB1 100ng/Kg -Intravenously injection -Treatment before I/R	-Increased expression levels of HIF1α -Decreased inflammatory response -Decreased infarct size	(H. C. Yao et al., 2016)
TLR4 mutant mice	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of cardiac HMGB1 -Decreased expression of inflammatory mediators -Attenuated ischemic injury	(Ding et al., 2012)
TLR4 mutant mice	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of cardiac HMGB1 -Decreased expression of inflammatory mediators -Attenuated apoptosis and decreased infarct size	(Ding et al., 2013)
Rat	I/R 30min I/2h R	-Endogenous (intracellular) HMGB1	-Decreased expression of cardiac HMGB1 by dexmedetomidine pre treatment -Decreased inflammatory response -Decreased infarct size - Inhibition of the HMGB1-TLR-4-MyD88-NF-κB signaling	(J. J. Zhang et al., 2017)
Rat	I/R 30min I/4h R	-Endogenous (intracellular) HMGB1	-Decreased expression of HMGB1 following IL33 pre-treatment -Decreased expression of inflammatory mediators and markers of cardiac injury -Attenuated apoptosis and decreased infarct size	(Ruisong et al., 2015)
Rat	I/R 40min I/2h R	-Exogenous BoxA 2mg/Kg -Intracardiac infusion -Treatment before R	-Synergistic effect of HMGB1 BoxA and miR-21 in attenuating cardiomyocyte apoptosis	(Q. Han et al., 2016)
Mouse	I/R Heart transplantation and 24h R	-Endogenous (intracellular) HMGB1	-Inhibited HMGB1 expression following overexpression of miR26a -Inhibited inflammatory cell infiltration and cytokine expression -Attenuated cardiac injury	(L. Yao, Lv, & Wang, 2016)
Rat	HF (MI)	-Exogenous HMGB1 2.5ug/rat -Intramyocardial injection -Treatment post-MI	-Reduced accumulation of dendritic cells -Reduced fibrosis and hypertrophy -Attenuated LV remodeling and improved cardiac function	(Takahashi et al., 2008)
Rat	HF (MI)	-Endogenous (extracellular) HMGB1	-Improved neovascularization following BMC transplantation -Increased circulating levels of HMGB1 -Reduced fibrosis and increased proliferation -Attenuated LV remodeling -Improved cardiac function -Macrophages polarization towards an anti-inflammatory phenotype (release of IGF1 and IL-10)	(Kaneko et al., 2013)
Mouse	HF (MI)	-Exogenous HMGB1 200ng/mouse -Intramyocardial injection -Treatment post-MI	-Cardiac regeneration and new blood vessel development -Reduced fibrosis -Attenuated LV remodeling and Improved cardiac function	(Limana et al., 2011)
Rat	HF (MI)	- Exogenous HMGB1 2.5ug/rat -Intramyocardial injection -Treatment post-MI	-Inhibited fibrotic pathway -Attenuated LV remodeling and Improved cardiac function	(He, Zhou, et al., 2013)
HMGB1-tg mice	HF (TAC)	-Endogenous (nuclear) HMGB1	-Preserved nuclear HMGB1 expression and attenuated DNA damage	(Funayama et al., 2013)

(*continued on next page*)

Table 1 (*continued*)

Species	Experimental mode	HMGB1	HMGB1-mediated effects	Ref
Mouse	HF (diabetic cardiomyopathy)	-Lentivector with shRNA-HMGB1 1 × 107 UT/30 μl -Intramyocardial injection -Treatment post-diabetes induction	-Prevented cardiac hypertrophy and cardiac dysfunction -Pharmacologic and genetic inhibition of HMGB1 -Decreased myocardial fibrosis -Attenuated LV remodeling and improved cardiac function	(Wang et al., 2014)
Mouse	HF (TAC)	-Exogenous HMGB1 200ng/mouse -Intramyocardial injection -Treatment before TAC	-Aggravated hypertrophy and cardiac dysfunction	(L. Zhang et al., 2016)

Gude and Sussman and Maroli and Braun (Gude & Sussman, 2018; Maroli & Braun, 2018).

Three years after our first report, Rossini and colleagues suggested a potential mechanism of HMGB1-mediated cardiac regeneration. They proved, by *in vitro* studies, that HMGB1 modulates ckit$^+$ cell migration and proliferation in a paracrine manner by exerting a chemotactic effect on cardiac fibroblasts and stimulating the release of several growth factors from these cells (Rossini et al., 2008). Specifically, in the conditioned media of HMGB1-stimulated human cardiac fibroblasts, they detected higher levels of cytokines, chemokines and angiogenic factors, including the vascular endothelial growth factor compared to non-stimulated ones. Accordingly, they found that these conditioned media stimulated the differentiation of ckit$^+$ cells toward an endothelial phenotype.

3.1.1.2. HMGB1 and angiogenesis. Indeed, the first demonstration of HMGB1-angiogenic properties was reported by Mitola and colleagues in 2006 (Mitola et al., 2006). In this study, the authors demonstrated that HMGB1 induced endothelial cell chemotaxis and proliferation *in vitro* and angiogenesis *in vivo* and these effects were inhibited by RAGE blockade. In 2007, Chavakis et al obtained similar results in endothelial progenitor cells (EPCs) demonstrating that HMGB1 stimulated adhesion and migration of these cells *in vitro* and promoted their homing to ischemic limbs *in vivo* (Chavakis et al., 2007). Results also indicated that RAGE represented the HMGB1 receptor mainly involved in the chemotactic activity of HMGB1 on EPCs further strengthening the data by Mitola et al.

In order to verify the angiogenic properties of HMGB1 in the infarcted myocardium, transgenic mice with cardiac-specific overexpression of HMGB1 (HMGB1-tg) were generated and MI was induced by coronary artery ligation (Kitahara et al., 2008). These mice showed improvement in survival and prevention of cardiac remodeling and dysfunction compared to wild-type mice. An enhancement in angiogenesis was detected as demonstrated by an increase in capillary and arteriole densities and these effects were mediated by paracrine mechanisms exerted by HMGB1 released into the circulation by necrotic cardiomyocytes. The same group recently demonstrated that HMGB1 released from the infarcted myocardium might mobilize bone marrow-derived cells to the ischemic heart and enhance their differentiation in EPCs as showed by their engraftment as vascular endothelial cells in new capillaries and arterioles (Nakamura et al., 2015). In both studies, the authors reported that their HMGB1-tg mice were characterized by relatively low levels of HMGB1 that could account for the observed beneficial effects since other groups have previously reported that high doses of this protein were deleterious (Kitahara et al., 2008; Nakamura et al., 2015).

3.1.1.3. HMGB1-mediated effects on LV remodeling. Interestingly, in 2009, Kohno et al confirmed the importance of the inflammatory response, when not excessive and persistent, for an appropriate healing process and the prevention of LV remodeling. Specifically, they firstly reported an association between elevated HMGB1 serum levels in patients with MI and adverse clinical outcome (Kohno et al., 2009) but, they also showed that, by blocking endogenous HMGB1 following MI in a rat model, the hearts were characterized on one end by an attenuation in post-MI inflammatory response but, on the other end, by a deterioration in function and in LV remodeling.

3.1.1.4. Role of HMGB1 on cardiomyocyte survival. Besides HMGB1 involvement in cardiac ckit$^+$ cell and EPC activation, it has been recently demonstrated a potential role of this protein in cardiomyocyte survival following acute MI (Foglio, Puddighinu, Germani, Russo, & Limana, 2016). Specifically, one of the mechanisms of HMGB1-mediated cardiac repair could be represented by the induction of autophagy and the attenuation of apoptosis. Autophagy is a process that results activated following acute MI in mice and has been demonstrated to exert protective effects on the heart (Schiattarella 2015; Nishida 2015). Indeed autophagy inhibition induces an aggravation in the remodeling of the left ventricle and cardiac performance (Kanamori et al., 2011; Sciarretta et al., 2012; X. Wu et al., 2014) while its up-regulation results in an attenuation of these processes (Buss, Riffel, Katus, & Hardt, 2010; X. Wu et al., 2014; Yan et al., 2005). Accordingly, our group showed that HMGB1 treatment, at least in part, enhanced cardiac function following acute MI in mice by an increase in autophagy and prevention of apoptosis (Foglio et al., 2016).

Nevertheless, another group suggested a direct correlation between apoptosis and HMGB1 levels. In a mouse model of acute MI in transgenic mice overexpressing the angiotensin-converting enzyme 2 (ACE2), the cardioprotective effect exerted by ACE2, i.e. decreased infarct size, attenuated apoptosis and improved cardiac function, was associated to the downregulation of circulating HMGB1 and of its associated downstream pro-inflammatory cytokines (Qi et al., 2016). Therefore, the authors attributed the beneficial effects of ACE2 to a reduction in inflammation in the infarcted myocardium. Nevertheless, measurements of cardiac functions and apoptosis were performed not during the acute phase but 4 weeks following MI, i.e. when the inflammatory response is resolved and the reparative process prevails.

Enhanced expression level of HMGB1 has been related also to another type of cell death, i.e. necroptosis, recognized as a well-characterized form of regulated cells necrosis. Specifically, in the aged heart, 1 week following MI, the beneficial effects of HGF on ckit$^+$ cells were mediated by the induction of necroptosis that facilitated cardiac repair by increasing HMGB1 expression and ckit$^+$ cell proliferation and differentiation. These effects lead to enhanced cardiomyocyte regeneration and angiogenesis and improved cardiac function 1 month following MI (J. Liu et al., 2016). Since treatment with Ad-HGF increased HMGB1 expression and necroptosis inhibition produced an opposite effect, the authors suggested that their data confirmed the results from our lab according to which HMGB1 enhances ckit$^+$ cell proliferation and differentiation after acute MI and suggested that this protein might mediate, at least in part, the beneficial effect of necroptosis.

3.1.1.5. Mechanism of HMGB1-mediated cardiac repair. Two studies tried to deepen the mechanism of HMGB1-mediated cardiac repair following

Table 2
Clinical values of HMGB1. hsCRP, high-sensitivity C-reactive protein; cTnI, cardiac troponin I; PCI, percutaneous intervention procedure; CAD, coronary artery disease.

Sample type	Assay	Results and prognosis	Ref
serum	Western Blot	Serum HMGB1 levels increased in patients with acute coronary syndrome compared to healthy subjects	(Goldstein et al., 2006)
serum	ELISA	Serum levels of HMGB1 as a predictor of adverse clinical outcome in patients with STEMI in the acute and late phase after MI	(Kohno et al., 2009)
plasma	ELISA	Increased HMGB1 plasma levels associated with impaired cardiovascular functional capacity in patients after acute MI	(Cirillo et al., 2009)
serum	ELISA	Increased HMGB1 serum levels correlated with autonomic dysfunction in patients in the acute phase of MI	(Giallauria et al., 2010)
serum	ELISA	Serum HMGB1 levels decreased 6 months after exercise-based cardiac rehabilitation in post-infarction patients with an attenuation in cardiac remodeling and an improvement of autonomic functions	(Giallauria et al., 2011)
serum	ELISA	Serum levels of HMGB1 were elevated in STEMI and NSTEMI patients and were strongly related with infarct size and LV function	(Andrassy et al., 2011)
serum	ELISA	Positive correlation between serum HMGB1 levels and the severity of HF in type 2 diabetic and non-diabetic patients	(Wang et al., 2011)
plasma	ELISA	Plasma HMGB1 levels as a prognostic biomarker in STEMI patients since its high levels predicted mortality when measured during the PCI procedure	(Sorensen et al., 2011)
plasma	ELISA	Increased HMGB1 plasma levels correlated with worsen LV function in HF patients with ischemic and non-ischemic cardiomyopathy	(Volz et al., 2012)
serum	ELISA	Strong correlation between serum HMGB1 levels measured on admission and cardiac death in patients with unstable angina and NSTEMI patients. Serum HMGB1 levels measured on admission represents a more effective means of early risk stratification than hsCRP	(Hashimoto et al., 2012)
serum	ELISA	Serum HMGB1 level as a predictor of disease severity in patients with acute MI or angina since it positively correlates with hsCRP and cTnI	(Yao et al., 2013)
serum	ELISA	Serum HMGB1 levels as an independent predictor of death in patients with chronic HF due to ischemic cardiomyopathy since they inversely correlated with LVEF and positively correlated with NT-pro-BNP during a 12-month follow-up	(Liu et al., 2015)
blood	FACS	HMGB1 expressed on circulating platelets and measured during the PCI procedure did not differ in patients with stable CAD and unstable CAD, NSTEMI and STEMI and did not correlate with outcomes.	(Rath et al., 2017)

acute MI. Zhou and colleagues suggested that HMGB1 treatment improved cardiac function in infarcted rat hearts by activating the Wnt/b catenin signaling pathway, known to be involved in post-MI healing and stem cell functions (X. Zhou et al., 2012). It should be noted that Zhou et al used the same experimental protocol used in our first report (Limana et al., 2005) but, in this case, coronary artery ligation was performed in rats and not in mice without any adjustment by weight of the dose of HMGB1 injected into the heart.

Our group, on the other hand, demonstrated the involvement of the Notch pathway (Limana et al., 2013). Specifically, in a mouse model of acute MI following HMGB1 treatment, Notch 1 signaling played a key role in HMGB1 ability to activate resident cardiac ckit$^+$ cells and the inhibition of this pathway impaired their proliferation and differentiation towards all cardiovascular cell lineages. Accordingly, in a more recent study, it has been demonstrated that Notch 1 signaling stimulated the differentiation of ckit$^+$NKX2.5$^+$ bone marrow stem cells into cardiomyocytes thus confirming the importance of this pathway in ckit$^+$ cell differentiation (R. Ding et al., 2015).

It is worth noting that a very recent study confirmed the role of HMGB1 in stem cell-mediated tissue repair showing its ability to accelerate tissue regeneration by targeting endogenous stem cells. Specifically, exogenous administration of a single dose of HMGB1 promoted the transition of CXCR4$^+$ skeletal, hematopoietic and muscle stem cells from G_0 to G_{Alert}, i.e a state in which stem cells enter the cell cycle more rapidly than quiescent stem cells leading to accelerated tissue repair (G. Lee et al., 2018a)

3.1.2. HMGB1 and ischemia/reperfusion

The effect of exogenous/endogenous HMGB1 in I/R injury has been widely addressed but the results and conclusions have been controversial: this is due to the high complexity of the I/R phenomenon that consists of two phases, both characterized by inflammation and HMGB1 influence.

Specifically, *ischemia* is associated with a rapid fall in ATP production, ROS production and cell function inhibition, among which cytosolic Ca^{++} accumulation and cell swelling, leading to cell damage of various severity (Kalogeris, Bao, & Korthuis, 2014; Raedschelders, Ansley, & Chen, 2012).

When *reperfusion* occurs, oxygen and substrates become available, producing an immediate metabolic reactivation with ATP increase and cell function restoration. Paradoxically, in many cells Ca^{++}-dependent functions are improperly activated with abundant ROS production, abnormal cytoskeleton contraction and protease system activation (proteasome, calpain, caspase and other Ca^{++}-dependent proteases) leading to a new wave of cell damage, from moderate stress to apoptosis and necrosis (Sanada, Komuro, & Kitakaze, 2011; T. Zhou, Chuang, & Zuo, 2015).

As a consequence, in this condition, a potent inflammatory response is progressively triggered by HIF1α and NF-κB activation. During *ischemia*, both transcription factors are activated following a rapid ROS increase produced by hypoxia (Cadenas, 2018; Loor & Schumacker, 2008); a number of HIF1α-dependent genes are transcribed, including alarmin receptors and other proinflammatory proteins; at the same time, the expression of NF-κB -dependent genes leads to a full inflammatory response and cell damage.

When *reperfusion* occurs a new burst of inflammation may be activated and potentiated by several factors with additive effects:

a) a further increase of ROS level associated to reperfusion-dependent metabolic reactivation (which contribute to a stronger activation of the HIF1α/NF-κB axis).

b) occurrence of reperfusion-dependent cell death (apoptosis and necrosis) (Kalogeris et al., 2014; Perrelli, Pagliaro, & Penna, 2011) which produce a new massive release of alarmins (especially HMGB1).

c) alarmins interact with pattern-recognition receptors (PPRs) on PPR-enriched cells (previously primed by hypoxia) producing a further increase in NF-κB activation.

Therefore, considering the I/R model, in order to interpret the different results when challenging the cell system with exogenous HMGB1, there is a crucial factor, other than the dose, that should be taken into account. This factor is the *timing of treatment* (before I or after I, just before R or following R).

3.1.2.1. Exogenous HMGB1 preconditioning. In 2008, Andrassy and colleagues reported for the first time that preconditioning with a high dose of HMGB1 was detrimental in a model of regional I/R. Specifically, they demonstrated that HMGB1, passively released from damaged or

inflammatory cells during ischemia and newly synthesized following reperfusion, participated to the pathogenesis of myocardial I/R injury by binding to RAGE and activating and sustaining an early inflammatory response that enhanced myocardial damage. In this study, wt and RAGE-/- mice were pretreated with recombinant HMGB1 (10ug/mouse i.p.) or HMGB1 BoxA and subjected to 30 min ischemia followed by 48 h reperfusion. Pretreatment with recombinant HMGB1 determined an increase in infarct size and in markers of tissue damage as TnT, TNFα and IL6 in wt animals while the HMGB1 BoxA injection reduced I/R injury. Interestingly, no differences were observed in RAGE-/- mice following administration of recombinant HMGB1 or HMGB1 antagonists confirming the importance of HMGB1-RAGE interactions in cardiac I/R injury. At the molecular level, they found that inhibition of HMGB1 decreased the phosphorylation of ERK1/2 and JNK and NF-κB binding activity (Andrassy et al., 2008).

Nevertheless, in the following years, two studies demonstrated that HMGB1-preconditioning in a rat model of I/R could decrease myocardial injury by inhibiting the inflammatory response and oxidative stress, as demonstrated by a decrease in circulating levels of inflammatory mediators and an increase in superoxide dismutase activities (Hu et al., 2010; D. Y. Zhang, Zhang, Zhou, Wang, & Yao, 2015). A main difference among these three studies is represented by the reperfusion interval adopted (longer in the study by Andrassy and colleagues than in the other two studies) that might explain the discrepancies among the results: a short reperfusion period might be not sufficient to detect the detrimental effects exerted by HMGB1.

Andrassy's group also described the role of HMGB1 in a long-term model of diabetes mellitus -induced post-ischemic remodeling. They confirmed, as in the previous study, that increased expression of HMGB1 present in a murine model of type 1 diabetes and its binding to RAGE sustained the inflammatory response that might contribute to myocardial dysfunction in this pathology. Also in this study, they adopted a long reperfusion period and a preconditioning setting but instead of using exogenous HMGB1, they inhibited the endogenous protein by HMGB1 BoxA since diabetes induced its expression (Volz et al., 2010).

3.1.2.2. Exogenous HMGB1 post-treatment. In the cardiac I/R model, only few studies investigated the effects of HMGB1 post-treatment. Oozawa and colleagues infused a neutralizing anti-HMGB1 mAb just before reperfusion in the rat heart since, in this experimental model, they have detected increased plasma levels of HMGB1 at 60 min following reperfusion. The authors did not find differences in hemodynamic variables in anti-HMGB1 mAb-treated rats compared to controls but they found, in the first group, an increased infarct size and an elevation in plasma level of troponin T and norepinephrine, two markers of cardiomyocyte damage. Therefore, they concluded that anti-HMGB1mAb treatment exacerbated I/R-induced myocardial damage mainly due to the effects of released HMGB1 in increasing interstitial norepinephrine concentration with no effect on I/R inflammation (Oozawa et al., 2008).

Similarly, another study, performed in isolated rat hearts, investigated the effects of a post-ischemic treatment with HMGB1 since, as indicated by the authors, several groups have previously reported that post-MI treatment with HMGB1 increased cardiac function and decreased LV remodeling. Interestingly, they used a low dose (200ng) and a high dose (1ug) of HMGB1, both infused just before reperfusion and compared their effects. Infusion of 200ng of HMGB1 determined lower levels of the pro-inflammatory cytokines TNFα, IL1 and IL6 or growth factors such as the vascular endothelial growth factor and IL10. This decrease was more pronounced using the greater dose of 1ug, but the beneficial functional effects, measured 1h following reperfusion, were not present indicating that a minimal level of inflammatory signal is required to counteract reperfusion injury and determine an improvement in function (Abarbanell et al., 2011). It should be reminded that HMGB1 is an early mediator of inflammation but, as an alarmin, following injury it also promotes activation of the innate immune system involved in the inflammatory reparative response. With respect to the heart and global I/R, this was the first study showing that early post-ischemic treatment with a low dose of exogenous HMGB1 was associated with improved functional recovery acutely supporting the concept that intervention in the first minutes following reperfusion is crucial for protecting the myocardium from I/R injury.

3.1.2.3. Effects of endogenous HMGB1 inhibition. Several other studies supported the initial finding of Andrassy regarding an involvement of HMGB1 in the worsening of myocardial I/R injury and, specifically, demonstrated that increased expression of HMGB1 correlated with increased cardiomyocyte apoptosis and other types of cell death. In particular, different drugs have been found to reduce cardiomyocyte apoptosis in I/R injury by inhibiting endogenous HMGB1 expression or activity. Among them glycyrrhizin (Zhai et al., 2012), minocycline (Hu et al., 2010), ethyl pyruvate (EP) (Lin, Chen, Li, & Fang, 2015a), hesperidin (X. Li et al., 2016), asperosaponin X (Jiang, Zhang, Zhu, & Hou, 2012) and celastrol (Tong, Zhang, Joseph, & Jiang, 2018) are included.

EP represents the first described pharmacological inhibitor of HMGB1 secretion (Ulloa et al., 2002) and differently from HMGB1 BoxA or anti-HMGB1 monoclonal antibody, is not expensive and its source is not limited. Since EP has been reported to inhibit HMGB1 release in several I/R models (Rabadi, Ghaly, Goligorksy, & Ratliff, 2012; Shen et al., 2013), Lin and colleagues hypothesized that this compound could exert a beneficial effect in a rat I/R model. Rats underwent 30 min ischemia and 48 h reperfusion and were treated, just before reperfusion, with EP or different doses of recombinant HMGB1 (1,10,100ug/Kg). Following EP treatment, the authors detected lower levels of HMGB1, TNFα and IL6 and a reduced cardiac dysfunction. All these effects were reversed when EP was co-administered with recombinant HMGB1 (at the highest dose) (Lin, Chen, Li, & Fang, 2015b). Very recently, another group demonstrated that EP retains its protective effect against myocardial I/R injury in rats even in hyperglycemia condition through the regulation of the HMGB1-RAGE/TLR- NF-κB pathway (Soh et al., 2018).

The flavanone hesperidin, whether used for pretreatment in rats undergoing I/R, attenuated cardiomyocyte apoptosis, the inflammatory response and oxidative stress by activation of the phosphatidylinositide 3-kinase (PI3K)/Akt pathway that led to a decrease in HMGB1 expression in the infarcted region of the LV. Accordingly, all these effects were reversed by the administration of a specific PI3K inhibitor (X. Li et al., 2016).

The involvement of the PI3K/Akt pathway in myocardial protection against HMGB1-mediated I/R injury has been demonstrated also in another study investigating the role of simvastatin, known to suppress inflammation independently of its lipid lowering effect, in a rodent model of cardiac I/R. Simvastatin pretreatment in rats undergoing I/R lowered serum levels of TNFα and cardiac troponin I and decreased myocardial expression of HMGB1 in a dose-dependent manner. These effects resulted in smaller infarct sizes following treatment that were reversed by using an inhibitor of PI3K (Q. F. Han et al., 2015). Recently, Zhu and colleagues suggested, in a letter to the Editor, an involvement of HMGB1/TLR4 pathway and endothelial cells in these effects since it is well known that statin plays a protective role toward these cells and HMGB1/TLR4 represents a pathway involved in the HMGB1-mediated endothelial cell permeability damage (Z. Zhu & Fang, 2016).

Noteworthy, in a rat model of I/R injury, pretreatment with HMGB1, by intravenous injection, resulted in the activation of HIF1α that, as a key factor in cellular adaptation to ischemia, exerted a cardioprotective effect by the PI3K/Akt pathway (Yao et al., 2016).

Two other studies explored the role of the *HMGB1-TLR4 axis* in triggering cardiomyocyte apoptosis during myocardial I/R injury. Since TLR4 is one of the receptors for HMGB1 that plays a crucial role in the induction of the inflammatory response, in the first study, the authors developed a TLR4-mutant mouse model where they performed 30min ischemia followed by 6 h reperfusion. Results showed that only few neutrophils infiltrated the myocardium after I/R and tissue structure

was maintained. Accordingly, the expressions of TNFα, IL8 and HMGB1 significantly decreased in mutant mice compared to controls (Ding et al., 2012b). In a following study, using the same mouse model and a similar experimental setting of I/R, the authors detected lower levels of apoptosis thus suggesting that the HMGB1-TLR4 axis might worsen myocardial I/R injury by inducing the inflammatory response and triggering cardiomyocyte apoptosis (H. S. Ding et al., 2013).

The HMGB1-TLR4 axis has been also involved in the cardioprotective effect in myocardial I/R injury of a highly selective α2-adrenergic receptor agonist, Dexmedetomidine (DEX), known to exert an anti-inflammatory effect in both sterile and infectious inflammation models (Y. Huang et al., 2014; Tan et al., 2015). Pretreatment with DEX attenuated the inflammatory response following I/R in rats by reducing myocardial HMGB1 release and inhibiting its downstream TLR4-MyD88-NF-κB signaling pathway (J. J. Zhang, Peng, Zhang, Meng, & Ji, 2017).

Recently, extracellular HMGB1 has been also correlated to the protective role of IL33 in myocardial I/R injury. IL33 has been demonstrated to attenuate cardiac remodeling via inhibition of the p38 MAPK and NF-κB pathways following acute MI and, most recently, in failing hearts (Veeraveedu et al., 2017; Yin et al., 2014). In this study, IL33 pretreated hearts presented a lower cardiac injury, as showed by lower serum levels of creatine kinase, lactate dehydrogenase and cardiac troponin I, and a smaller infarct size compared to controls. Most importantly, IL33 markedly inhibited apoptosis. Since the I/R group was characterized by reduced expression of HMGB1, TNFα and IFNγ and increased expression of phospho-p38, the authors suggested that IL33 attenuated inflammation and apoptosis, and therefore protect against I/R injury, by inhibition of HMGB1 release (Ruisong et al., 2015).

3.1.2.4. HMGB1 and cardiomyocyte autophagy. As in the setting of acute MI, also in the model of I/R, HMGB1 has been demonstrated to induce autophagy. During myocardial I/R injury, the induction of autophagy may be protective during ischemia and detrimental during reperfusion by promoting cardiomyocyte survival or contributing to cardiomyocyte cell death, respectively (Matsui et al., 2007a; Matsui et al., 2007b). In an *in vitro* model of hypoxia and reoxygenation, it has been demonstrated that HMGB1 treatment, just before hypoxia, induced and sustained autophagy in rat neonatal cardiomyocytes as showed by increased expression levels of Beclin-1 and LC3 (W. Xu, Jiang, Hu, & Fu, 2014). A recent study confirmed these results, both *in vitro* and *in vivo*, showing that endogenous HMGB1 is able to promote apoptosis and epithelial to mesenchymal transition (EMT) in cardiomyocytes following hypoxia/reoxygenation (H/R) injury by inducing autophagy through the upregulation of the tyrosine kinase receptor discoidin domain receptor 1, and the downregulation of mTOR phosphorylation (Ouyang et al., 2016). In this study, it is not clear why EMT activation should increase H/R injury since EMT is a biological process involved in tissue fibrosis, as the authors claimed, but also in the generation of cardiac progenitor cells and therefore in myocardial repair and regeneration (Germani, Foglio, Capogrossi, Russo, & Limana, 2015).

3.1.2.5. miRNAs involved in HMGB1-mediated I/R injury. Very recently, the role of different small non-coding RNA molecules (miRNAs) in HMGB1-mediated cardiac injury during I/R has been investigated. Almost all the studies demonstrated a protective role of different miRNAs in cardiac I/R injury by inhibition of HMGB1 expression that resulted in attenuation of cardiomyocyte apoptosis and inflammatory response (Q. Han, Zhang, Zhong, Zhang, & Chen, 2016; Y. Wang, Ouyang, Wang, & Jian, 2016; Xie et al., 2016; L. Yao, Lv, & Wang, 2016). Among *in vivo* studies, Han and colleagues investigated whether myocardial apoptosis could be modulated by treatment, immediately before reperfusion, with recombinant HMGB1 BoxA and antagomiR21, since different reports have already demonstrated that, in the context of I/R injury, the blockade of extracellular HMGB1 functions was beneficial and pretreatment with miR21 attenuated cardiomyocyte apoptosis. Accordingly, better outcomes were obtained by treatment with recombinant HMGB1 BoxA alone than in association with antagomiR21 demonstrating a synergistic effect between HMGB1 BoxA and miR21 (Q. Han et al., 2016).

Conversely, a recent report showed that HMGB1 contributes to a reduction in myocardial I/R injury in a miRNA dependent manner. Specifically, HMGB1 is a direct target of miR410, involved in mitophagy after cardiac ischemia/reperfusion injury. In this study, MiR-410 expression was significantly increased in H/R-stimulated cultured human adult cardiomyocytes and its overexpression caused defective mitophagy in these cells. Functional analysis demonstrated that HMGB1 overexpression in this culture system improved cell viability and mitochondria function by modulating the heat shock protein β1 activity (F. Yang, Li, Dong, & Mi, 2018).

3.2. HMGB1 and HF

Inflammation plays a role also in the pathogenesis of HF. Specifically, failing hearts are characterized by a low-grade inflammation and this sustained activation of inflammatory signaling contributes to LV remodeling evidenced by collagen degradation and progressive LV dilation. Nevertheless, despite encouraging preclinical studies, results of clinical trials of anti-cytokine therapy have been discouraging. For instance, clinical trials targeting the inflammatory mediator tumor necrosis factor (TNF) in patients with HF have provided negative findings (Mann, 2015), showing a worsening of clinical outcomes (Chung et al., 2003; Mann et al., 2004). A possible explanation is that TNF exerts not only deleterious but also cytoprotective effects as demonstrated by several experimental studies performed during acute MI (Kurrelmeyer et al., 2000; Lecour et al., 2002). Hence, it is reasonable that, in the setting of HF, TNF antagonism might result mainly in the loss of its beneficial effects. Moreover, the stimulation of endogenous ckit$^+$ cells with cytokines or growth factors might represent an effective approach to repopulate and restore old scarred tissue in failing hearts, therefore, reducing further myocardial scarring and expanding the working myocardium.

Different animal models of HF have been used to study the effects of HMGB1 on LV remodeling: HF induced by MI and HF induced by diabetes or after transverse aortic constriction (TAC).

3.2.1. HF induced by MI

Takahashi et al. studied the therapeutic efficacy of HMGB1 intramyocardial injection in chronically infarcted rat hearts (Takahashi et al., 2008). Four weeks after administration, they found an attenuated LV remodeling. Specifically, they detected a reduction in fibrosis and cardiomyocyte hypertrophy and when they tried to identify the molecular mechanism underlying HMGB1-mediated cardioprotection, they found activation of ERK1/2, an important survival factor for cardiomyocytes. Interestingly, they did not find differences in capillary density and infarct size between the two groups of animals and they were not even able to detect any myocardial regeneration as we detected in our first study (Limana et al., 2005). Therefore, they attributed the improvement in cardiac function following HMGB1 treatment to attenuated ventricular remodeling related to a modulation of the local inflammatory response, i.e. reduced accumulation of dendritic cells. According to the authors, the reasons for the discrepancies between their results and our results (Limana et al., 2005) rely essentially on the different experimental model (chronic HF *vs* acute MI) and type of rodent used (rat *vs* mouse) despite the use of an equivalent amount of HMGB1 injected in the LV wall.

More recently, the same group investigated the potential role of HMGB1 in the recovery of failing hearts following bone marrow mononuclear cell (BMC) transplantation. In particular, the cardioprotective effect of transplanted BMCs was attributed to the extracellular HMGB1 released from dead donor cells (Kaneko et al., 2013). In this report, differently from the previous one, the authors detected in the hearts transplanted with BMC not only reduced collagen deposition but also neovascularization and increased proliferation that determined an

improvement in cardiac function. These effects were mediated by the HMGB1-stimulated polarization of macrophages toward an anti-inflammatory phenotype. Interestingly, in recent years, different studies have come to similar conclusions showing that stem cell transplantation into the infarcted heart contributes to the recovery of cardiac function, in part, by switching macrophages from a pro-inflammatory to an anti-inflammatory and reparative phenotype through secreted factors such as IGF-1 and interleukin (IL) 10 (de Couto et al., 2015; van den Akker, de Jager, & Sluijter, 2013).

Few years later the first report by Takahashi and colleagues, our group used a mouse model of HF and the same experimental protocol of Takahashi et al, i.e. intramyocardial injection of the same amount of exogenous HMGB1 3 weeks following MI and measurement of cardiac function and LV remodeling 4 weeks following treatment (Limana et al., 2011). In treated hearts, compared to controls, we detected an enhancement in cardiac function and an attenuation in LV remodeling but, differently from Takahashi et al, we associated these effects with myocardial regeneration and new blood vessel development. We tried to deepen the mechanism of HMGB1-mediated attenuation of LV remodeling and we found a decreased collagen deposition, as showed by Takahashi, and an increased collagenolytic activity mediated by miR-206 inhibition of TIMP-3 expression. We hypothesized that these effects could have facilitated the migration of resident ckit^{+} cells in the scar of failing hearts as evidenced by the presence of a thin band of small cardiomyocytes.

More recently, another study confirmed that HMGB1 treatment prevented LV remodeling and improved cardiac function in a rat model of chronic HF and these effects were mediated by the inhibition of the fibrotic pathway (Y. He, Zhou, et al., 2013). The experimental protocol was identical to the one used in the two previous studies and, also in this case, markers of cardiac remodeling were analyzed. Treated hearts were characterized by a reduced extracellular matrix deposition possibly mediated by the inhibition of the transforming growth factor-β/Smad signaling pathway. It is interesting to note that inhibition of a fibrotic pathway might support alternative reparative pathways as regeneration.

3.2.2. Role of nuclear and extracellular HMGB1 in HF induced by diabetes or aortic constriction

Aside from the effects of exogenous HMGB1, there is an interesting report that analyzed the importance of nuclear HMGB1 in the development of HF. Since oxidative stress induced by pressure overload contributes to cardiac DNA damage and ventricular dysfunction in failing hearts (Siggens, Figg, Bennett, & Foo, 2012), the authors hypothesized that nuclear HMGB1 could play a protective role by preventing DNA damage. Using transgenic mice overexpressing cardiac specific HMGB1, they demonstrated that nuclear HMGB1 levels after TAC were higher in transgenic mice compared to WT mice and, most importantly, DNA damage was attenuated and cardiac hypertrophy and HF were prevented, confirming that maintenance of nuclear HMGB1 level in the heart prevented cardiac dysfunction after pressure overload (Funayama et al., 2013).

Nevertheless, not all rodent studies have reported good result, even though, in the following reports, the experimental models are completely different from the previous ones (heart failure induced by diabetes or aortic constriction vs heart failure induced by MI; extracellular HMGB1 *vs* nuclear HMGB1). For instance, in an independent study, Wang et al hypothesized a role of HMGB1 as a proinflammatory cytokine in myocardial fibrosis associated with diabetic cardiomyopathy, since a previous study has already demonstrated that HMGB1-specific blockage significantly reduced post-MI remodeling in mice with type 1 diabetes mellitus (Volz et al., 2010). To test this hypothesis, they induced diabetes in mice by streptozotocin and inhibited the expression of HMGB1 by lentivirus-mediated short-hairpin RNA. They firstly verified that HMGB1 was diffusely expressed in the myocardium of diabetic mice and demonstrated that HMGB1 inhibition determined an improved cardiac function and attenuated LV remodeling. These effects were mediated by a decreased myocardial fibrosis (W. K. Wang et al., 2014). Recently, in a letter to the Editor, Zhu and colleagues suggested an implication of endothelial cells in HMGB1-mediated cardiac fibrosis associated with diabetic cardiomyopathy since vessel dysfunction characterizes diabetes and ischemia-induced cardiomyopathy (Z. Zhu & Hu, 2017).

In another study, since the HMGB1 expression is increased in the myocardium under pressure overload, the authors hypothesized a role of extracellular HMGB1 in the development of pressure overload-induced cardiac hypertrophy and HF (L. Zhang et al., 2016). They induced TAC and performed an intramyocardial injection of recombinant HMGB1 in mice. Results demonstrated an aggravation of TAC-induced cardiac hypertrophy and cardiac dysfunction following treatment, as demonstrated by functional studies and histological analysis. Nevertheless, all these pathological changes could be reversed by HMGB1 inhibition most likely due to an attenuated local inflammation. These results seem to disagree with the results described by Funayama et al. (Funayama et al., 2013). Nevertheless, Funayama studied nuclear HMGB1, while in this report the function of extracellular HMGB1 has been investigated. Further, pressure overload triggers the release of HMGB1 from cardiomyocytes and an increase of intracellular HMGB1 expression with its translocation from the nucleus to the cytoplasm; this translocation might cause DNA damage, increasing the severity of cardiac hypertrophy. Therefore, it is reasonable that exogenous HMGB1 may be involved in pressure overload-induced cardiac remodeling.

Very recently, the cardiac dysfunction present in aging hearts has been also associated to HMGB1-mediated inflammation. Specifically, using a mouse model of aging heart, it has been suggested that the M1 macrophage polarization could activate the HMGB1-TLR2/TLR4 signaling pathways and, therefore, leads to the inflammatory response and the following cardiac dysfunction (Karuppagounder et al., 2016).

3.3. HMGB1 as clinical biomarker

Since HMGB1 has been identified as a critical mediator of inflammation in the early phase of MI, following its passive release by necrotic cells and, in the subsequent phase of LV remodeling, following its active release by mononuclear cells, different clinical studies have shown that this protein may represent a highly attractive biomarker in patients with coronary artery diseases either during the acute phase and the late phase in post-infarction patients. Specifically, all these studies indicated an association between high HMGB1 levels (Yamada et al., 2006) and impaired outcome. Goldstein and colleagues firstly demonstrated that HMGB1 was significantly increased in the serum of patients with acute coronary syndrome as compared with healthy subjects (Goldstein et al., 2006). The group of patients enrolled in this prospective cohort study was very small but few years later another study showed, in 54 patients early after acute MI, increased HMGB1 plasma levels that were associated with impaired cardiovascular functional capacity as showed by cardiopulmonary and Doppler-echocardiography indices (Cirillo et al., 2009). The same group also demonstrated, in patients following MI, a close association between increased HMGB1 levels and autonomic dysfunction represented by the fall in heart rate during the first minute after exercise, a powerful predictor of mortality (Giallauria et al., 2010). Therefore, HMGB1 might represent not only a marker of damage and inflammatory response but a critical player in promoting myocardial dysfunction. Based on the fact that an appropriate inflammatory response is fundamental for the prevention of LV remodeling, while an excessive and persistent inflammation might induce myocardial vulnerability, these authors also showed that HMGB1 levels in post-infarction patients after 6 months of exercise-based cardiac rehabilitation were significantly decreased compared to untrained patients and this reduction was associated to an attenuation

in cardiac remodeling and the improvement of autonomic functions (Giallauria et al., 2011).

In the same year, Andrassy and collaborators demonstrated, for the first time, that elevated HMGB1 levels were closely related both to infarct size and LV function in patients with ST-elevation (STEMI) and non-ST-elevation (NSTEMI) (Andrassy et al., 2011). Interestingly, Kohno et al. previously suggested that serum HMGB1 levels could represent a predictor of adverse clinical outcomes and LV dysfunction in patients with STEMI not only in the early phase but also in the late phase after MI (Kohno et al., 2009).

A larger clinical study pointed out that circulating HMGB1 levels might represent a prognostic biomarker in a highly homogeneous group of STEMI patients since HMGB1 levels independently predicted mortality when measured during the percutaneous intervention procedure even after adjustment for age, sex, troponin I, and creatine kinase-myocardial band (Sorensen, Pedersen, Mogelvang, Skov-Jensen, & Flyvbjerg, 2011). Accordingly, in another study that enrolled 258 patients with unstable angina and NSTEMI patients, serum levels of HMGB1, measured on admission, were strongly associated with cardiovascular mortality (Hashimoto et al., 2012). Noteworthy, Hashimoto and colleagues found that measurements of serum HMGB1 on admission showed a better ability to separate high- and low-risk patients and, therefore, represented a more effective means of early risk stratification than high-sensitivity C-reactive protein. Noteworthy, HMGB1 resulted independently associated with cardiovascular mortality similarly to troponin I but since these two markers reflect different aspects of acute coronary syndrome pathophysiology, the authors suggest that their combination may allow risk stratification for adverse outcome in different groups of patients with unstable angina and NSTEMI. The superior prognostic value of HMGB1 compared to high-sensitivity C-reactive protein may have resulted, as already suggested by Giallauria et al, from its unique ability to self-amplify and prolong the inflammatory response. These results were confirmed by another study performed on patients with stable and unstable angina pectoris as well as acute MI (H. C. Yao et al., 2013). Therefore, HMGB1, by identifying patients at a high risk of cardiovascular death, might be helpful in the treatment of these patients.

Finally, a very recent study examined the specific role of platelet-derived HMGB1 in patients with stable coronary artery disease, unstable coronary artery disease, NSTEMI and STEMI since platelets are the major source of HMGB1 within arterial thrombi (Vogel et al., 2015). Results showed that HMGB1 expressed on circulating platelets and measured during the percutaneous intervention procedure did not differ in these patients and did not significantly correlate with outcomes neither with troponin I nor with creatine kinase-myocardial band (Rath, Geisler, Gawaz, & Vogel, 2017).

The diagnostic and prognostic value of HMGB1 in HF has not been extensively investigated. Due to the elevated mortality rates for HF, a great interest exists in identifying additional biomarkers that allow early detection or implicate prognosis of this clinical syndrome. Three studies evaluated HMGB1 in HF patients (Liu, Zhang, Zhang, et al., 2015; Volz et al., 2012; L. J. Wang et al., 2011).

Wang et al firstly found a positive correlation between HMGB1 and the severity of HF in type 2 diabetic and non-diabetic patients. Specifically, they associated elevated levels of HMGB1, the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and RAGE-related proteins with HF but described decreasing HMGB1 levels in HF patients with diabetes. Therefore, according to these results, HMGB1 could not be considered selective for inflammatory processes related to HF in the presence of other comorbidities (L. J. Wang et al., 2011).

Nevertheless, a more recent study analyzed HMGB1 levels in HF patients with ischemic and non-ischemic cardiomyopathy and results demonstrated that these levels increased in HF patients and positively correlated with NT-proBNP, a definite indicator for HF, and with worsen ventricular function (Volz et al., 2012). Lately, Liu and colleagues enrolled patients with chronic HF due to ischemic cardiomyopathy and found that HMGB1 could be considered an alternative marker in the risk stratification of patients with chronic HF since it inversely correlated with LVEF and positively correlated with NT-proBNP. Noteworthy, both HMGB1 and NT-proBNP represented an independent predictor for death during a 12-month follow-up (Liu et al., 2015). In a letter to the Editor, Dr. Zhu's group has suggested that endothelial cells might mediate the effects of HMGB1 in chronic HF Z. Zhu, Hu, et al., 2015) but, most likely, mechanisms and cell types involved in HMGB1 mediated pathophysiologic process in ischemic heart diseases are multiple and further studies should be carried out to better dissect the role of HMGB1.

4. Conclusions and perspectives

The role of extracellular HMGB1 remains controversial in the field of cardiovascular diseases. HMGB1 is an alarmin and therefore, under stress conditions, signals danger to other cells and triggers inflammation, but it also activates an inflammatory reparative response. Sometimes, very striking differences in its levels have been observed, depending on cellular context and tissue pathological conditions. Additionally, it has been demonstrated that HMGB1 does recruit not only cells of the innate immune system but also stem cells (and somatic cells, reprogrammed or remodeled by hypoxia), and by activating them, is able to induce tissue regeneration. Nevertheless, if inflammation is not resolved but persists, HMGB1 can intensify the inflammatory response and exacerbate injury. With respect to experimental models of heart diseases, the balance between detrimental *vs* protective (double-edged) effects depends also on different conditions, i.e. dose, animal model, experimental setting, timing of administration as well as duration/degree of extracellular HMGB1 upregulation.

In the setting of acute MI, a large amount of HMGB1 is actively secreted from inflammatory cells and passively released from necrotic cardiomyocytes. Nevertheless, different studies have demonstrated that a low dose of HMGB1 administered when its expression is still low, i.e. in the early phase post-MI, mediates repair and regeneration by enhancing cardiomyocyte survival and activating resident stem cells. These effects contribute to an improvement in both structural and functional outcomes after MI.

In the post MI heart failure model, a low-grade pathological chronic inflammation is perpetuated via TLR4 signaling which is responsible for the activation of NF-κB and the subsequent expression of a wide range of pro-inflammatory genes. In this context, treatment with a low dose of HMGB1 might represent an important tool to attenuate LV remodeling by modulating the local inflammatory response. This modulation can be achieved also by HMGB1-mediated stimulation of endogenous cardiac progenitor cells since several studies have suggested that these cells are able to modulate the inflammatory state of macrophages from pro-inflammatory to anti-inflammatory within the myocardium leading to a long-term improvement in cardiac function (de Couto et al., 2015).

With respect to global cardiac I/R, there is a complex situation due to the presence of an excessive and persistent inflammation that causes further tissue damage. Reperfused myocardial infarction is associated with a potent inflammatory response that leads firstly to the recruitment of leukocytes and then of monocytes and lymphocytes in the ischemic area. This inflammatory response is much more severe during reperfusion injury than after permanent ligation. So, in this case, it is likely that the timing (pre-ischemic *vs* post-ischemic) and the dose of HMGB1 are crucial factors in determining cardioprotective or deleterious effects of HMGB1 in the damaged heart. In particular, in this model, preconditioning with a high dose of HMGB1 might exacerbate injury, as confirmed by almost all the studies performed using an experimental model of myocardial I/R injury. Further, in most studies, reperfusion was performed for no longer than 48h but at this time point repair has just started and, therefore, a longer follow up should be used in rodents. Nevertheless, it is important to stress that, in the clinic, reperfusion injury is not so relevant since a prompt revascularisation of

the ischemic myocardium results in definite clinical benefits by minimizing the dimensions of MI, reducing the degree of left ventricular dysfunction and improving survival rates (Reed, Rossi, & Cannon, 2017).

It has been previously demonstrated that HMGB1 presents different redox forms acting on different receptors and either promoting inflammation or regeneration. Interestingly, it exerts one of these two processes by switching among different redox forms (Bianchi et al., 2017). A mutant (3S), characterized by the replacement of cysteines with serines (resistant to oxidation), has been recently created. This mutant behaves as the reduced form of HMGB1 by binding directly to CXCR4 and results showed that it is more effective than the WT protein in promoting regeneration without exacerbating inflammation following both muscle and liver injury (Tirone et al., 2018). Differences in the regenerative effects of the mutant 3S compared with the reduced form of HMGB1 were not observed in the study performed on multiple tissues by Lee and colleagues (Lee et al., 2018b). Nevertheless, it would be very interesting to determine whether the 3S/CXCR4 axis safely accelerate cardiac regeneration compared to the fully reduced form, therefore, expanding its translational benefit.

From a clinical point of view, post-infarction patients are quickly reperfused with percutaneous transluminal coronary angioplasty or thrombolysis. Therefore, as in the experimental model of I/R, HMGB1, released by inflammatory cells recruited during reperfusion, might amplify the inflammatory response exerting detrimental effects on cardiac function. Accordingly, all the clinical studies reported a positive correlation between increased HMGB1 levels and worsen ventricular function.

Probably, a number of contradictory aspects may depend on/could be explained by the experimental/clinical condition analyzed, chiefly, on time elapsed from obstruction to reperfusion, on temperature and on basic metabolic conditions (ischemia is not only hypoxia but also shortage of metabolic substrate and reduced catabolite elimination).

Thus, HMGB1 might represent an attractive potential biomarker due to its role as a danger signal that senses cell damage, but whether its inhibition could represent a successful therapeutic approach is difficult to predict. In preclinical studies, different HMGB1 inhibitors, such as EP, glycyrrhizin and hesperidin, have been found to reduce cardiomyocyte apoptosis, decrease the infarct size and to improve cardiac function. However, the pathophysiologic heterogeneity of the human condition lead to hypothesized that not all patients may benefit from targeted inhibition of inflammation, as demonstrated by different clinical trials (Gislason et al., 2006; Giugliano, Giugliano, Gibson, & Kuntz, 2003; Sholter & Armstrong, 2000; Timmers et al., 2007) and for this reason personalized therapies are needed. In this respect, however, HMGB1 could represent a biomarker extremely valuable in identifying patient subpopulations with specific pathophysiologic disturbances.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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