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REVIEW ARTICLE

High-Mobility Group Box 1, Oxidative Stress, and Disease

Daolin Tang, Rui Kang, Herbert J. Zeh III, and Michael T. Lotze

Abstract

Oxidative stress and associated reactive oxygen species can modify lipids, proteins, carbohydrates, and nucleic acids, and induce the mitochondrial permeability transition, providing a signal leading to the induction of autophagy, apoptosis, and necrosis. High-mobility group box 1 (HMGB1) protein, a chromatin-binding nuclear protein and damage-associated molecular pattern molecule, is integral to oxidative stress and downstream apoptosis or survival. Accumulation of HMGB1 at sites of oxidative DNA damage can lead to repair of the DNA. As a redox-sensitive protein, HMGB1 contains three cysteines (Cys23, 45, and 106). In the setting of oxidative stress, it can form a Cys23-Cys45 disulfide bond; a role for oxidative homo- or heterodimerization through the Cys106 has been suggested for some of its biologic activities. HMGB1 causes activation of nicotinamide adenine dinucleotide phosphate oxidase and increased reactive oxygen species production in neutrophils. Reduced and oxidized HMGB1 have different roles in extracellular signaling and regulation of immune responses, mediated by signaling through the receptor for advanced glycation end products and/or Toll-like receptors. Antioxidants such as ethyl pyruvate, quercetin, green tea, N-acetylcysteine, and curcumin are protective in the setting of experimental infection/sepsis and injury including ischemia-reperfusion, partly through attenuating HMGB1 release and systemic accumulation. *Antioxid. Redox Signal.* 14, 1315–1335.

Introduction

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage (6, 43). ROS have also been identified as important signaling molecules in various pathways regulating both cell survival and cell death (25, 201). High-mobility group box 1 protein (HMGB1) is a highly conserved nuclear protein, acting as a chromatin-binding factor that bends DNA and promotes access to transcriptional protein assemblies on specific DNA targets (133, 150). In addition to its nuclear role, HMGB1 also functions as an extracellular signaling molecule and damage-associated molecular pattern molecule (DAMP) (17, 131, 183), during inflammation (133, 243, 254), cell differentiation (145, 204), cell migration (48, 54, 157, 159, 181), cell proliferation (68, 122, 159, 176, 211), tissue regeneration (61, 122, 172, 233), and tumor development (49, 95, 129, 130, 132, 219, 225, 269). In this review, we focus on the role of HMGB1 in oxidative stress and antioxidant strategies based on targeting HMGB1.

Oxidative Stress, ROS, and Redox Signaling

ROS are free radicals that contain the oxygen atom. These very small molecules include superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$) (Fig. 1). They are highly reactive due to the presence of unpaired valence shell electrons. ROS form as a natural byproduct of the normal metabolism of oxygen and have important physiological roles in signal transduction, but in excess can contribute to the mechanisms of disease by dysregulation of signal transduction and/or by oxidative damage to cellular macromolecules (lipids, proteins, DNA, RNA, and carbohydrates) that exceeds the cellular capacity for regeneration or repair (29, 249). The major cellular source of ROS is generated by mitochondrial and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. $O_2^{\bullet -}$ is produced by the electron transport chain on the inner mitochondrial membrane, and the rate of production is dependent on mitochondrial potential. In the presence of mitochondrial superoxide dismutase (SOD), $O_2^{\bullet -}$ can be converted to H_2O_2, which can then diffuse out of the mitochondria into the cytoplasm. In the presence of high iron concentrations, H_2O_2 can form the highly reactive $O_2^{\bullet -}$ *via* the Fenton reaction. Catalase is responsible for converting H_2O_2 to water and oxygen. $O_2^{\bullet -}$ can also react with nitric oxide (NO) to form the highly reactive peroxynitrite ($ONOO^{\bullet}$). In animals, ROS can influence cell signaling cascades, including protein tyrosine phosphatases (PTPs), tyrosine kinases (PTKs), protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and nuclear factor (NF)-κB (78).

The DAMP Laboratory, Department of Surgery, G.27 Hillman Cancer Center, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania.

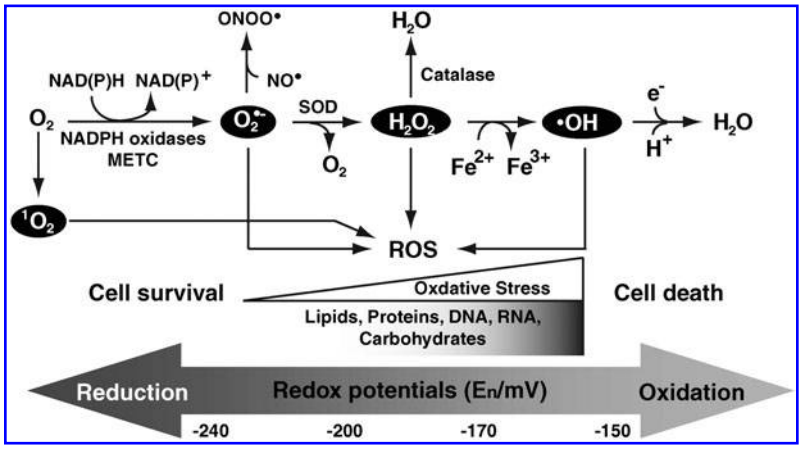

FIG. 1. Generation of free radicals. Superoxide can be generated by specialized enzymes, such as the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases or as a byproduct of cellular metabolism, particularly the mitochondrial electron transport chain (METC). During mitochondrial respiration some electrons go directly to oxygen-forming superoxide anion ($O_2^{\bullet -}$) that leads to the production of other free radicals such as peroxynitrite ($ONOO^{\bullet}$) through reaction with nitric oxide ($NO^{\bullet}$), hydrogen peroxide (H_2O_2) through enzymatic dismutation by superoxide dismutase (SOD), and hydroxyl radical ($^{\bullet}OH$) by Fenton reaction. Singlet oxygen ($^1O_2$) is the diamagnetic form of molecular oxygen (O_2). Redox potentials related to these cellular processes are adapted (189).

Redox signaling is the process wherein free radicals, ROS, and other electronically activated species act as messengers in biological systems (251). All forms of life maintain a reducing environment within their cells. This reducing environment is preserved by enzymes that maintain the reduced state through a constant input of metabolism-derived energy. The redox environment within the mitochondrial intermembrane space is maintained separately from the cytosol and matrix (78). Increased and/or sustained levels of oxidative stress and related mediators play a major role in most chronic human diseases, including atherosclerosis (22), diabetes (94), cardiovascular diseases (66), cancer (16), neurodegenerative disorders (14), and chronic liver (246) and lung (161) diseases. Inflammation is a host defense activated by exogenous (*i.e.*, pathogen-associated molecular patterns) or endogenous danger signals (*i.e.*, DAMPs) (131, 134). Inflammation is deeply entangled with redox modulation (28). Triggering of pattern recognition receptors on inflammatory cells induces ROS generation. As a consequence, activated cells mount antioxidant responses to counteract the possible harmful effects of oxidation. When repair is completed, homeostasis is restored. Growing evidence indicates that intra- and extracellular redox affects protein structure, secretion, and function of cytokines such as transforming growth factor beta 1 (13), interleukin-1 (IL-1) (24), IL-4 (199), IL-10 (250), S100 proteins (70), tumor necrosis factor (TNF) (202), and HMGB1 (100, 134, 183). Moreover, Redox also regulates pattern recognition receptors such as the Toll-like receptors (TLRs), and the receptor for advanced glycation endproducts (RAGE) expression and function (35, 91, 151). The thiol-disulfide oxidoreductase thioredoxin-1 (Trx1) (195) and NO (101) are secreted by leukocytes and regulate extracellular redox. Redox of SOD1 in turn regulates caspase-1 and IL-1 release in the setting of endotoxic shock (143). In addition, apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1) is a multifunctional protein involved in reduction and oxidation regulation of HMGB1-induced inflammatory responses (266). Thus, reduction/oxidation of pathogen-associated molecular patterns, DAMPs, and PPRs regulates immunity and inflammation.

Oxidative Stress, Autophagy, Apoptosis, and Necrosis

As a major source of ROS production, mitochondria are especially prone to ROS-mediated damage. Such damage can induce the mitochondrial permeability transition caused by opening of nonspecific high conductance permeability transition pores in the mitochondrial inner membrane. ROS themselves also provide a signal leading to the induction of autophagy, apoptosis, and necrosis (Fig. 2).

Macroautophagy (subsequently referred to simply as autophagy) is the sequestration of organelles and long-lived proteins in a double-membrane vesicle, called an autophagosome or autophagic vacuole, inside the cell (106). The primary function of autophagy is to recycle cellular components to sustain metabolism during nutrient deprivation and to prevent the accumulation of damaged, toxic proteins, and organelles during stress. In most situations, autophagy promotes survival in response to stress and starvation. Mitochondrial quality control is important in maintaining proper cellular homeostasis. Selective mitochondrial degradation by autophagy (mitophagy) is suggested to have an important role in quality control (224, 261). Indeed, many stimuli that induce ROS generation also induce autophagy, including nutrient starvation, mitochondrial toxins, and hypoxia (193). ROS formation in the mitochondria is a fundamental regulatory event promoting autophagy and mitophagy (102, 192). The major endogenous source of cellular ROS is the mitochondrial electron transport chain (192). ROS can induce autophagy through several distinct mechanisms involving catalase or caspase activation of autophagy-related gene 4 (Atg4) and disturbances in the mitochondrial electron transport chain (11). Nip3-like protein X (Nix) and Atg32 are mitochondrial proteins that confer selectivity during mitophagy in erythroid cells and yeast, respectively (97, 187).

Chaperone-mediated autophagy (CMA), a selective mechanism for degradation of cytosolic proteins in lysosomes, contributes to the removal of altered proteins as part of the cellular quality-control systems (99). In CMA, only those proteins that have a consensus peptide sequence are recognized by the binding of a heat shock protein 70 (HSP70)-containing chaperone/co-chaperone complex. This CMA substrate/chaperone complex then moves to the lysosomes, where the CMA receptor lysosome-associated membrane protein type-2A (LAMP-2A) recognizes it. The protein is unfolded and translocated across the lysosome membrane assisted by the lysosomal hsc70 on the other side (99). Induction of mild-oxidative stress in cells increases the degradation of proteins *via* CMA (99, 103). Part of the enhanced CMA directly results from the oxi-

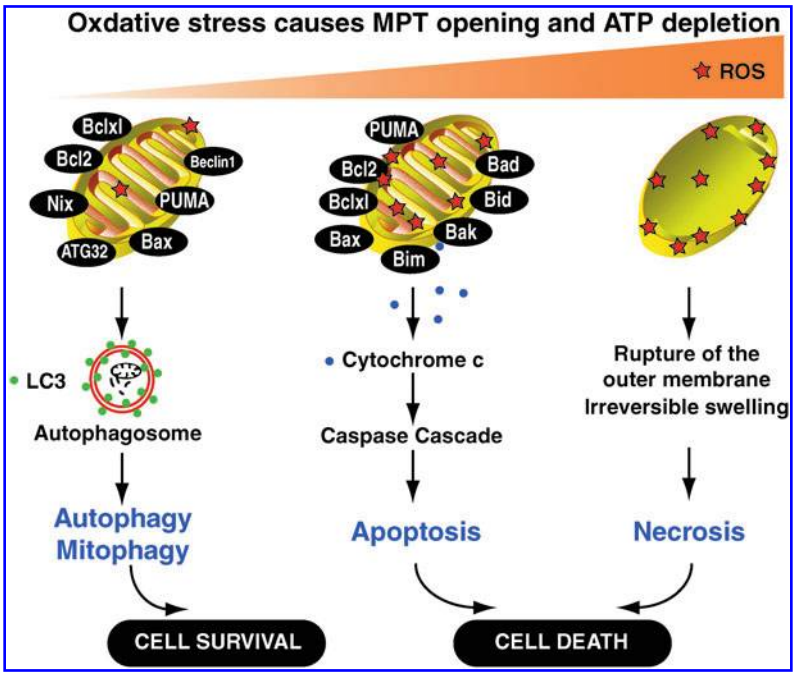

FIG. 2. Pathways activated in response to different degree of oxidative stress. When low oxidative stress is just enough to lead to the mitochondrial permeability transition (MPT), and autophagy and mitophagy are likely induced (261). As the oxidative damage increases, molecules such as cytochrome c may be released from mitochondria activating the caspase cascade and triggering apoptosis. At the extreme, oxidative stress causes severe MPT or even the rupture of the mitochondrial membrane, and neither autophagy nor apoptosis can provide an adequate response. The Bcl-2 proteins are a family of proteins involved in the response to autophagy and apoptosis, and play important roles in regulating MPT. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

dative modification of the CMA substrates, which are more readily degraded through this pathway, when compared with their unmodified counterparts (99, 103). It is possible that partial unfolding, typically associated with oxidative damage, could expose hidden CMA-targeting motifs, facilitating their recognition by the cytosolic chaperone complex (99).

Excessive ROS production and adenosine triphosphate depletion from uncoupling of oxidative phosphorylation promotes necrotic cell death. Release of cytochrome c (Cyt c) after mitochondrial swelling activates caspases and initiates apoptotic cell death (193, 261) (Fig. 2). Bcl-2 family members (antiapoptotic [*i.e.*, Bcl-2 and Bcl-XL] or pro- apoptotic [*i.e.*, Bax, Bid, Bad, Bim, Bak, NOXA, and the p53-upregulated mediator of apoptosis, PUMA]) (179) play important roles in regulation of the mitochondrial outer membrane permeabilization and MPT (Fig. 2). Both Bcl-2 and Bcl-XL negatively regulate Beclin1-dependent autophagy (152, 163). In addition, PUMA itself can induce autophagy that leads to the selective removal of mitochondria. This function of PUMA depends on Bax/Bak and can be reproduced by overexpression of Bax (260). Cytoskeletal reorganization is also an important regulator of apoptosis and autophagy (20, 64, 149, 174). Recently, WAVE1, an actin cytoskeleton regulator, was found to be associated with mitochondrial Bcl-2, and its depletion led to mitochondrial release of Bcl-2, and phosphorylation of Bcl-2 (96). Depletion of WAVE1 expression increased anticancer drug-induced production of ROS in leukemia cells (96). It is not clear whether WAVE1 is involved in autophagy and/or mitophagy.

Cysteine and Disulfide Bonds

Cysteine is uniquely suited to sensing a range of redox signals as the thiol side-chain (-SH) can be oxidized to several different reversible redox states such as disulphide (R-S-S-R); sulphenic acid (R-SOH); and S-nitrosothiol (R-SNO). Importantly, not all cysteines are equally reactive. The protein environment of the thiol has a key role in determining this reactivity by affecting the ionization state of the thiol (the thiolate ion is much more reactive to peroxides than the protonated form) and its overall accessibility (65).

Disulfide bonds play an important role in the folding and stability of proteins, particularly those secreted into the extracellular medium (197). Disulfide bonds in proteins are formed after oxidation of the thiol groups of cysteine residues (Fig. 3). The other sulfur-containing amino acid (AA), methionine, cannot form disulfide bonds. More aggressive oxidants convert cysteine to the corresponding sulfinic acid and irreversibly oxidized sulfonic acid. Cysteine residues play a valuable role by crosslinking proteins, which increases the rigidity of proteins and also functions to confer proteolytic resistance. Since protein export is a bioenergetically costly process, minimizing its necessity is advantageous. Inside the cell, disulfide bridges between cysteine residues within a polypeptide support the protein's secondary structure.

Redox Sensors

Redox sensors were first described in bacteria, including the OxyR and SoxR redox-sensitive transcription factors, the chaperone molecule Hsp33, the oxygen sensor FNR, and others (Fig. 4). All of these redox receptors have a structure designed

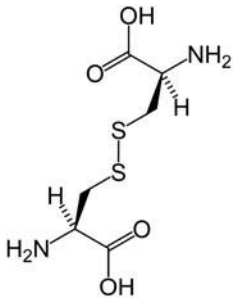

FIG. 3. Cystine is composed of two cysteines linked by a disulfide bond. Rarely is it found as a free amino acid, but rather as a consequence of proteolysis.

to sense specific ROS, oxidants, or other reactive intermediates. These ancestral redox sensors can essentially contribute to rapid mechanisms designed to deal with ROS and to make critical adjustments allowing survival of the bacteria. During evolutionary development, these simple bacterial sensors have been replaced with more specifically designed proteins, such as yeast thiol peroxidases (enzymes belonging to the family of peroxyredoxins or GPXs), transcription factor Yap1 (9), and Rap2.4a (198), which contribute to ROS signaling. In mammals, the hypoxia-inducible transcription factors (8), Cyt c (247), nuclear factor-erythroid-2-related factor 2 (212), the type 2 chloride intracellular channel (86), the transient receptor potential melastatin (140), phosphatase and tensin homolog (34), RAGE (35), and HMGB1 (77, 185) regulate ROS-homeostasis by sensing cellular redox status (Fig. 4).

Zinc/cysteine coordination environments in proteins are redox-active. Oxidation of the sulfur ligands mobilizes zinc, whereas reduction of the oxidized ligands enhances zinc binding, providing redox control over the availability of zinc ions (137). Iron also is utilized as a sensor of cellular redox status. Iron-based sensors incorporate Fe-S clusters, heme, and mononuclear iron sites, acting as switches to control protein activity in response to changes in cellular redox balance (156). Moreover, there are significant interactions between calcium and redox species, and these interactions modify a variety of proteins that participate in signaling transduction pathways and in other fundamental cellular functions that determine cell life or death (73).

HMGB1 Basics

The HMG-1 protein was first purified from nuclei ~40 years ago and termed HMG protein because of its rapid mobility on electrophoresis gels (62). HMG-1 was subsequently renamed HMGB1 by a nomenclature committee (26). It is constitutively expressed in many types of cells, and a large pool of preformed HMGB1 is stored in the nucleus owing to the presence of two lysine-rich nuclear localization sequences (21). As a DNA chaperone, HMGB1 participates in DNA replication, recombination, transcription, and repair. HMGB1 also interacts with and enhances the activities of a number of transcription factors including p53 (12, 89, 130, 142, 208), p73 (209, 235), the retinoblastoma protein (45, 90), members of the Rel/NF-κB family (3, 23), and nuclear hormone receptors including the estrogen receptor (38, 51, 239, 271). *HMGB1*-gene-deficient mice are born with several defects and die shortly after birth of hypoglycemia initially believed to be caused by deficient glucocorticoid receptor function (27). In addition to its nuclear role, HMGB1 also functions as an extracellular signaling molecule during inflammation, immunity, cell differentiation, cell migration, and tissue regeneration (46, 49, 133, 150) (Fig. 5).

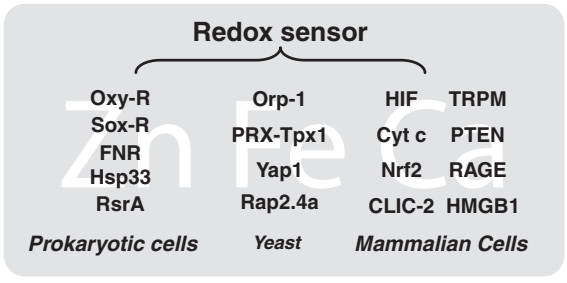

FIG. 4. Examples of redox sensors in prokaryotic cells, yeast, and mammal cells. There are significant interactions between zinc (Zn), iron (Fe), calcium (Ca), and redox species.

Structure of the Redox-Sensitive HMGB1 Protein

HMGB1 is a 215-AA protein of ~30 kDa. Structurally, HMGB1 is composed of three domains: two positively charged domains (A box and B box) and a negatively charged carboxyl terminus (the acidic tail). HMGB1 adopts a closed, dynamic but compact conformation, shown by nuclear magnetic resonance spectroscopy and small angle X-ray scattering (207). The long acidic tail of HMGB1 protein forms an extended and flexible structure that interacts with specific residues within and between the HMG boxes (107). Moreover, the C-terminal acidic tail has a higher affinity for the B box and that A box–tail interactions are preferentially disrupted (207). Functionally, the A and B boxes are DNA-binding domains. HMG-box proteins are targeted to particular DNA sites in chromatin by either protein–protein interactions or recognition of specific DNA structures. Recombinant analysis shows that the B box contains cytokine activity by inducing macrophage secretion of proinflammatory cytokines (116). This cytokine activity is antagonized by the recombinant A box. The first 21-AA residues (AA89–109) of the recombinant B box represent the minimal peptide sequence that retains cytokine-like activity (116). The protein structure involved in binding of HMGB1 with RAGE is located between AA residues 150 and 183. A recent study suggests that the C-terminal acidic tail is responsible for the inhibitory effects of HMGB1 on efferocytosis (11).

Three cysteines are encoded at positions 23, 45, and 106 (Fig. 6). These two Cys23-Cys45 residues can rapidly form an intramolecular disulfide bond with the standard redox potential as low as −237 mV. This suggests that the cellular glutathione system alone is not enough to keep HMGB1 completely reduced within the cell (185). The reduction of oxidized HMGB1 by thioredoxin is sufficient to maintain most of the HMGB1 in a reduced form, whereas the reaction is far slower than other reducing reactions mediated by thior-

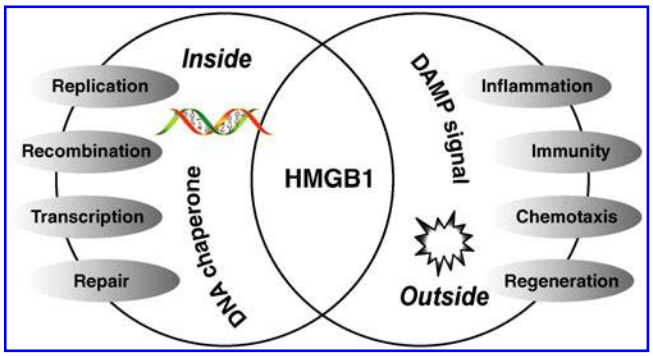

FIG. 5. Functions of high-mobility group box 1 (HMGB1). HMGB1 is present in almost all metazoans and plants. As a DNA chaperone, HMGB1 participates in DNA replication, recombination, transcription, and repair. HMGB1 is passively released from necrotic cells and is actively secreted by inflammatory cells, mediating the response to inflammation, immunity, chemotaxis, and tissue regeneration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

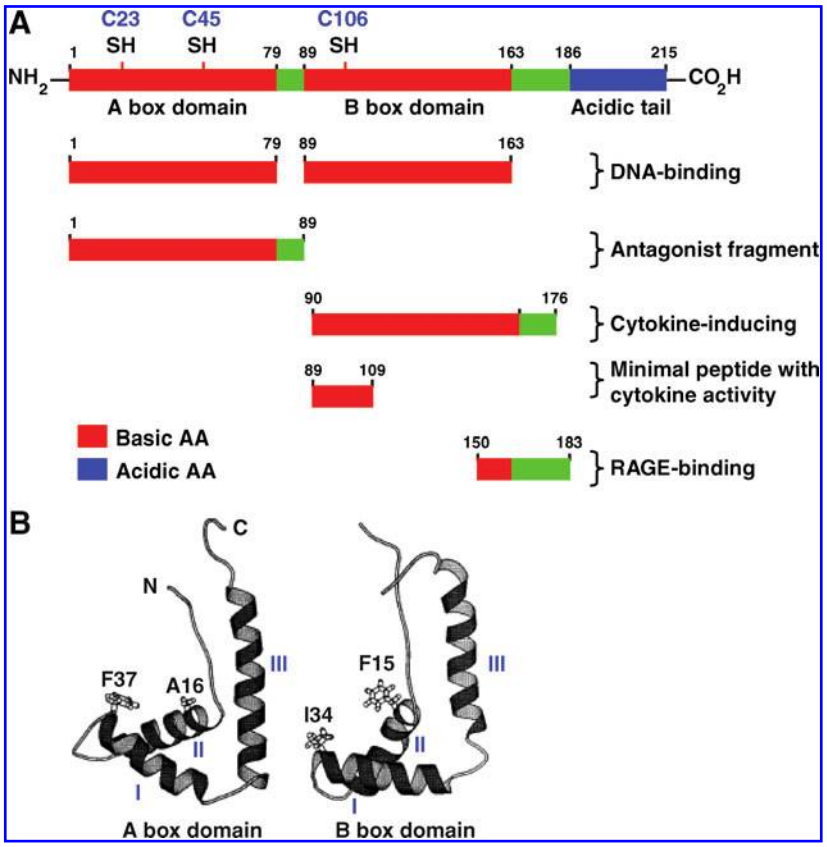

FIG. 6. Structure of the HMGB1 protein. (**A**) HMGB1 is a conserved chromosomal protein composed of two similar DNA binding domains (A and B box) linked by a short basic stretch to an acidic C-terminal tail of 30 residues. There are oxidation-sensitive unpaired cysteines at positions 23, 45, and 106. (**B**) Helical secondary structure of A box domain and B box domain (226). Green shades are neutral amino acids; red-shaded amino acids are basic and blue-shaded amino acids are acidic residues. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

edoxin. The low efficiency of the thioredoxin–HMGB1 reaction, together with the protein stabilization by the Cys23-Cys45 disulfide bond, might lead to accumulation of the oxidized form of the HMGB1 protein in cells under oxidative stress (185). Replacement of Cys23 and/or 45 with serines did not affect the nuclear distribution of the mutant proteins, whereas C106S and triple cysteine mutations impaired nuclear localization of HMGB1 (77), allowing some of the protein entry to the cytosol. C106 is required for HMGB1 binding to TLR-4 and activation of cytokine release in macrophages (256). These various functional domains of HMGB1 are retained conservatively in many species, suggesting multiple critical roles in its biological function intracellularly and extracellularly, precluding changes in the molecule.

Our recent studies demonstrated that HMGB1 promotes autophagy and cell survival in cancer chemotherapy and nutrition depletion (214, 215, 220). Reduced exogenous HMGB1 increases autophagy and oxidized HMGB1 increases apoptosis (214, 220). Mutation of cysteine 106, but not the vicinal cysteines 23 and 45, of HMGB1 promotes cytosolic localization and sustained autophagy (215). Moreover, the intramolecular disulfide bridge (C23/45) of HMGB1 is required for binding to Beclin 1 and sustaining autophagy (215). These findings suggest that redox of HMGB1 regulates autophagy.

HMGB1 and Oxidative DNA Damage Repair

HMGB1 proteins are constitutively expressed in the nucleus of both cancer and normal cells. HMGB1's affinity for a number of different DNA structures has been measured. In addition to supercoiled, single-stranded, B- and Z-DNA, it binds preferentially to DNA mini-circles, four-way junctions, looped structures, hemicatenated DNA, and triplex DNA (87, 113, 153, 254). Native HMGB1 extracted from tumor cells inhibits DNA replication and this effect is reduced after acetylation and completely abolished after removal of the acidic C-terminal tail. Recombinant HMGB1, however, fails to inhibit replication, but it acquires this property after *in vitro* phosphorylation by PKC (229). A nuclear protein complex containing HMGB1 and HMGB2, Hsp70, ERp60, and glyceraldehyde-3-phosphate dehydrogenase is involved in the cytotoxic response to DNA modified by incorporation of anticancer nucleoside analogs (110), suggesting that HMGB1 plays a critical role in DNA repair. Accumulation of HMGB1 is found at sites of oxidative DNA damage in live cells, thus defining HMGB1 as a component of an early DNA damage response (167). Reduced histone acetylation after DNA damage in HMGB1-deficient cells indicates a role for HMGB1 in DNA damage-induced chromatin remodeling (112). Mutations in mitochondrial DNA and oxidative stress both contribute to aging, which is the greatest risk factor for neurodegenerative diseases (123). It is not clear what the role of HMGB1 is in mitochondrial DNA mutation although HMGB1 can localize in mitochondria during human endothelial cell *Toxoplasma gondii* infection (210). Recent studies have identified the cross-link of HMGB1 with a DNA base excision repair intermediate, indicating that this protein is involved in base excision repair pathway (63, 128). Moreover, HMGB1 facilitates trinucleotide repeat CAG expansion by stimulating APE1 and flap endonuclease 1 in forming single strand breaks and ligatable nicks (127, 128). However, the molecular mechanisms underlying its effect on flap endonuclease 1 remain to be elucidated.

Active Secretion and Passive Release of HMGB1

Immune cells actively release HMGB1 in response to exogenous bacterial products (such as endotoxin or CpG-DNA) (84, 241) or endogenous host stimuli (*i.e.*, TNF, IFN-γ, or H_2O_2) (175, 221, 222). Cytolytic cells, both natural killer (NK) cells and specific T-cells, induce HMGB1 release from melanoma cell lines (83). The redox potential in the endoplasmic reticulum (ER), where most extracellular proteins become oxidized before secretion, is −180 mV (185, 191). If HMGB1 is secreted through the ER, 99% of the released HMGB1 should be in the oxidized form in equilibrium. HMGB1 lacks a leader peptide and is thus not secreted *via* the classical ER-Golgi secretory pathway (241). HMGB1 secretion from monocytes/macrophages depends on relocalization from the nucleus to special cytoplasmic organelles, the secretory lysosomes (21, 59, 175). Unless the vesicle provides an environment as oxidative as the ER, both reduced and oxidized forms may exist when HMGB1 molecules are released into the extracellular space. The released HMGB1 in the reduced form should be a short-lived species because of the extracellular oxidative environment (185). However, the reduced extracellular microenvironment generated by cysteine and redox enzymes, possibly secreted by stressed cells (184) or passively released by necrotic cells, prevents the oxidation of HMGB1, prolonging its extracellular lifespan and activity (28). Notably, these two forms of HMGB1 likely have different roles in extracellular signaling (133, 164).

The initial phase of HMGB1 secretion requires an inflammatory signal such as lipopolysaccharide (LPS), IL-1, or TNF to the monocyte (241). This signal will lead to acetylation of lysine residues, which causes an accumulation of HMGB1 in the cytoplasm and blocks reentry to the nuclear compartment (21). In addition, serine phosphorylation might be another requisite step for HMGB1 nucleocytoplasmic translocation (263). The phosphorylation of HMGB1 is potentially also mediated by the calcium/calmodulin-dependent protein kinase IV (272) because calcium/calmodulin-dependent protein kinase IV can be translocated to the nucleus after endotoxin stimulation, where it can potentially bind and phosphorylate HMGB1 (272). In addition, HMGB1 can be passively released from necrotic cells (190) or cells infected by viruses (*i.e.*, West Nile, salmon anemia, dengue, and influenza viruses) or mycobacteria (67, 76) and similarly triggers inflammatory response. *In vitro*, apoptotic cells activate macrophages to release HMGB1 (169). Monoclonal antibodies directed against HMGB1 conferred protection against organ damage but did not prevent the accumulation of apoptotic cells in the spleen. Thus, HMGB1 production is downstream of apoptosis on the final common pathway to organ damage in severe sepsis (169).

HMGB1 has been shown to bind to at least five different surface receptors expressed on immune cells, namely, the receptor for advanced glycosylation endproducts (RAGE) (95, 173, 206), TLR-2 (264), TLR-4 (139, 264), triggering receptor expressed on myeloid cells-1 (52), and CD24 (30). After interaction they activate MAPKs, NF-κB, and phosphoinositide 3-kinases/AKT signaling pathways (Fig. 7). The absence of HMGB1 severely impairs the activation of TLR-3, TLR-7, and TLR-9 by their cognate nucleic acids (254). HMGB proteins

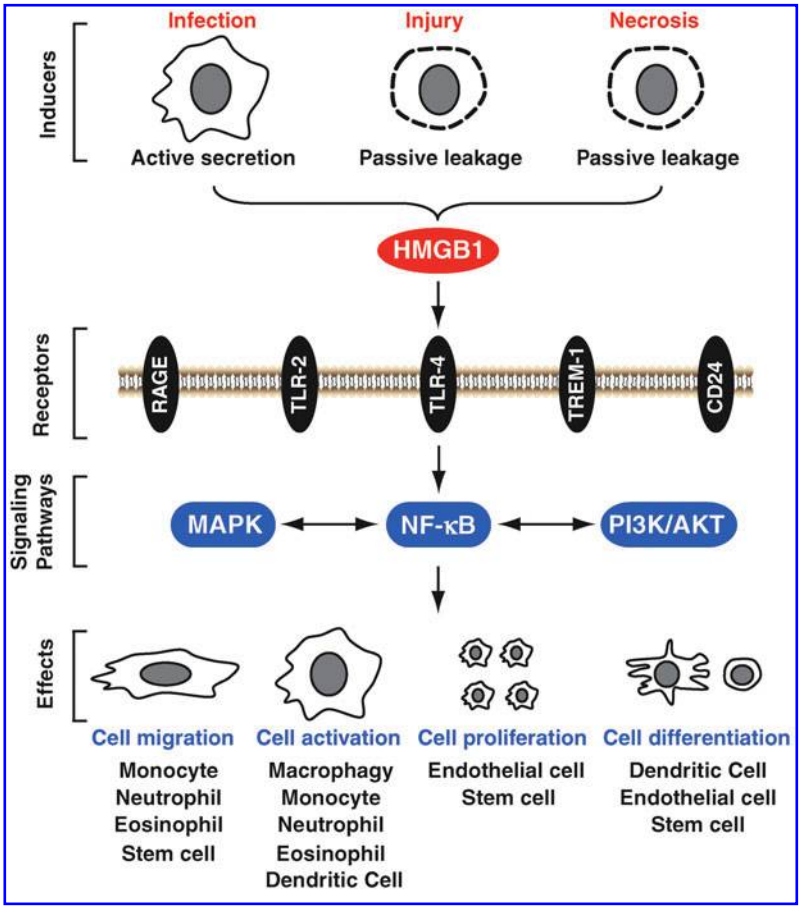

FIG. 7. Extracellular HMGB1 functions as a damage-associated molecular pattern molecule signal. HMGB1 is passively released from injury and necrotic cells and is actively secreted by inflammatory cells, binding with high affinity to several receptors, including the receptor for advanced glycation end products (RAGE), Toll-like receptors (TLR)-2, TLR-4, triggering receptor expressed on myeloid cells-1 (TREM-1), and CD24, mediating the response to cell migration, cell activation, cell proliferation, and cell differentiation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

function as universal sentinels for nucleic-acid-mediated innate immune responses (254).

Once released, extracellular HMGB1 mediates a wide range of biological responses in diverse cell types and tissues. *In vitro*, extracellular HMGB1 can activate macrophages and monocytes (4), and promote dendritic cell (DC) maturation (47, 147, 182). *In vivo*, HMGB1 causes acute lung inflammation and epithelial-cell barrier leaking (2, 188). Moreover, increased levels of HMGB1 are found in patients with sepsis and other major inflammatory diseases, including rheumatoid arthritis and meningitis (213, 223, 241). Accumulating evidence indicates that HMGB1 is capable of stimulating migration of neurite (54), smooth muscle cells (41), tumor cells (79), mesoangioblast stem cells (158), monocytes (181), DCs (255), and neutrophils (155, 242). HMGB1 could interact with phosphatidylserine on cell surface of apoptotic neutrophils and consequently inhibit phagocytotic elimination of apoptotic neutrophils by macrophages (125). Notably, HMGB1 is capable of attracting stem cells (159) and may be important for skeletal muscle, heart tissue repair, and regeneration (42, 61, 119, 180). *In vitro*, HMGB1 induces migration and proliferation of both adult and embryonic mesoangioblasts, and disrupts the barrier function of endothelial monolayers (159). Moreover, HMGB1 induces human primary cardiac fibroblasts migration and proliferation (180). HMGB1 is capable of stimulating differentiation of DC (47), erythroleukemia cell (205), neuroblastoma cell (162), myoblasts (177), and endogenous cardiac stem cell (122).

Hsp72 Inhibits HMGB1 Release and Function in Oxidative Stress

ROS are produced as a normal product of cellular metabolism. In particular, one major contributor to oxidative damage is H_2O_2, which is converted from superoxide that leaks from the mitochondria. H_2O_2 induces both active and passive HMGB1 release from macrophage and monocyte cultures in a time- and dose-dependent fashion (222). At nontoxic doses, H_2O_2 induced HMGB1 cytoplasmic translocation and active release within 3–24 h. At higher concentrations, however, H_2O_2 exhibits cytotoxicity for macrophages and monocyte cell cultures, and subsequently triggers both active and passive HMGB1 release. In addition, H_2O_2 stimulates interaction of HMGB1 with a nuclear export factor, chromosome region maintenance 1 (CRM1) protein homolog, in macrophage/monocyte cultures. Inhibitors specific for the c-jun N-terminal kinase, MEK-extracellular signal-regulated kinase (ERK), but not p38 MAPKs, abrogate H_2O_2-induced active HMGB1 release (222). These findings establish an important role for oxidative stress in inducing active HMGB1 release potentially through an MAPK- and CRM1-dependent mechanism (Fig. 8).

Representing a universal response to diverse adverse stimuli, cells rapidly express stress-inducible HSPs such as Hsp90, Hsp70, Hsp60, and Hsp27 (75). As major stress-inducible proteins, the Hsp70 family consists of ubiquitous Hsp73 and Hsp72 inducible by heat shock, oxidative stress, and infection. Intracellular Hsp72 functions as a molecular chaperone to maintain cellular homeostasis (71, 75, 146). Nuclear Hsp72 confers a protective role against various environmental stressors (36, 50, 238, 248). Hsp70 inhibits apoptosis downstream of Cyt c release and upstream of caspase-3 (60, 115). Hsp70 with LAMP-2A mediates the so-called CMA (31, 37).

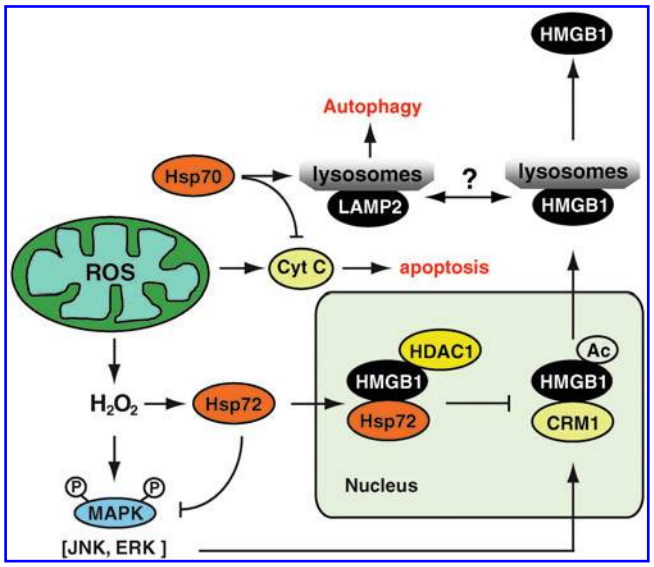

FIG. 8. Hsp72 regulates oxidative stress-induced HMGB1 cytoplasmic translocation and release. Upon stimulation with oxidative stress (*i.e.*, H_2O_2), mitogen-activated protein kinase (MAPK) signal pathways are activated to trigger potential acetylation of HMGB1. On the other hand, oxidative stress also induces nuclear translocation of Hsp72, which directly or indirectly interacts with various nuclear proteins (such as HMGB1 and histone deacetylase-1 [HDAC1]) within the nucleus. The Hsp72-facilitated potential recruitment of HDAC1 to HMGB1 may consequently prevent HMGB1 acetylation, cytoplasmic translocation, and subsequent release *via* the secretory lysosome pathway. Hsp70 inhibits apoptosis downstream of cytochrome c release and with LAMP-2A drives chaperone-mediated autophagy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

Notably, enhanced expression of Hsp72 (by gene transfection) renders murine macrophage cell lines resistant to H_2O_2-induced HMGB1 cytoplasmic translocation and release. In response to oxidative stress, cytoplasmic Hsp72 translocates to the nucleus, where it interacts with nuclear proteins, including HMGB1, and prevented oxidative stress-induced HMGB1 cytoplasmic translocation and release (216) (Fig. 8). Moreover, overexpression of Hsp72 inhibits CRM1 translocation and interaction between HMGB1 and CRM1 in macrophages after LPS or TNF-α treatment (217). In addition, overexpression of Hsp72 strongly inhibited HMGB1-induced cytokine expression and release, which correlates closely with (i) inhibition of the MAPKs (p38, c-jun N-terminal kinase, and ERK), and (ii) inhibition of the NF-κB pathway (Fig. 9). These findings suggest that Hsp72 plays an important role in the regulation of HMGB1 release and proinflammatory function in the setting of oxidative stress.

TLR-4 Mediates HMGB1-Induced ROS Production

NADPH oxidase is a highly regulated membrane-bound enzyme complex that catalyzes the production of superoxide by the single electron reduction of oxygen, using NADPH as the electron donor. The core enzyme is comprised of both membrane-bound (*i.e.*, gp91phox and p22phox) and cytosolic (*i.e.*, p40phox, p47phox, p67phox, and rac-1/2) components.

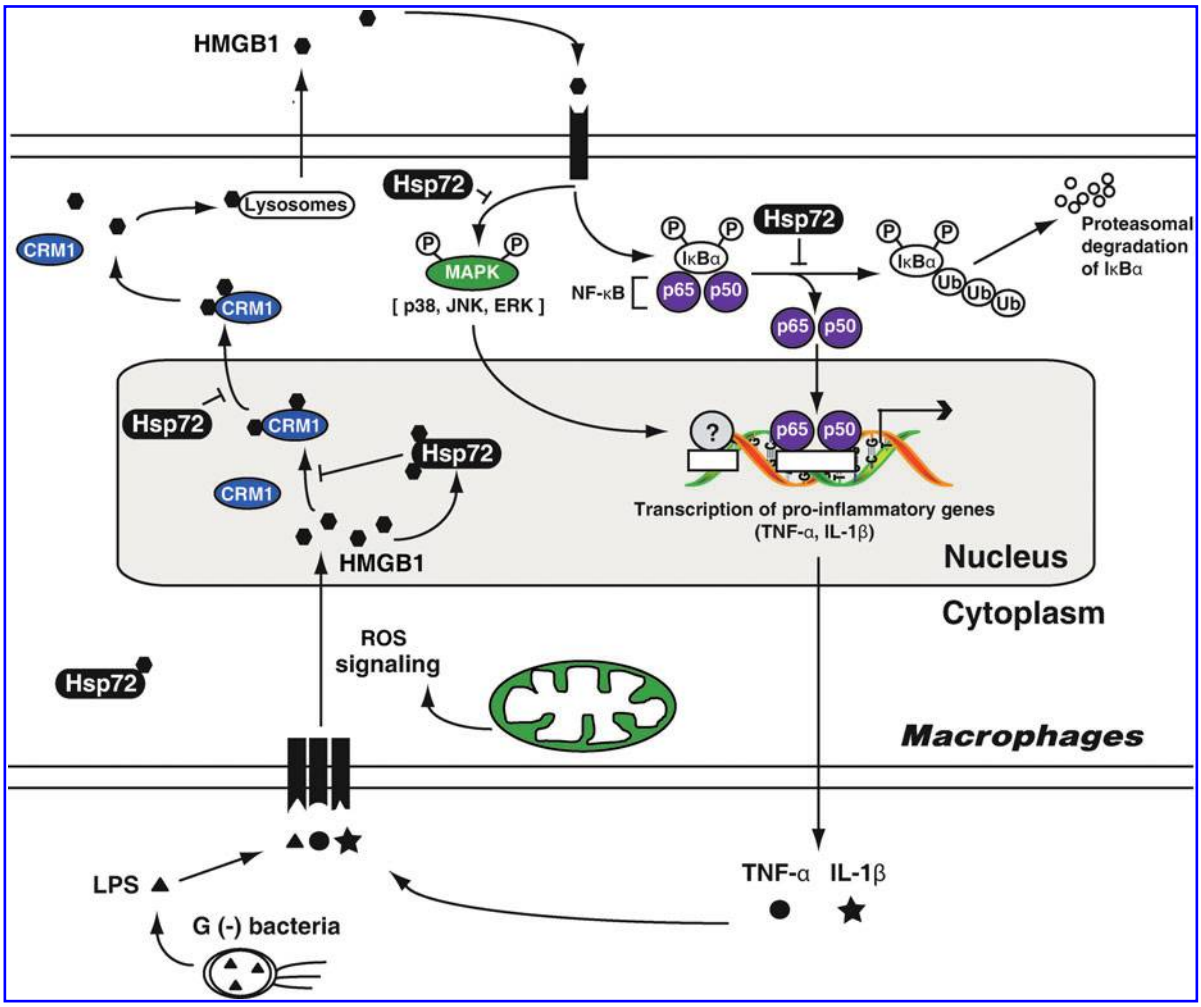

FIG. 9. Hsp72 is an important intracellular protein to inhibition of HMGB1 release and proinflammatory function in macrophages (217). Hsp72 attenuates lipopolysaccharide (LPS)- or tumor necrosis factor (TNF)-α-induced HMGB1 release partly through inhibiting chromosome region maintenance 1 (CRM1)-dependent nuclear export pathway of HMGB1. Hsp72 also inhibits HMGB1-induced cytokine (*i.e.*, TNF-α and interleukin [IL]-1β) expression and release potentially by inhibiting MAPKs and nuclear factor (NF)-κB activation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

Upon stimulation, receptor-mediated activation of the oxidase complex leads to activation of secondary signaling intermediates, culminating in the phosphorylation and recruitment of the cytosolic components to the membrane-bound molecules to assemble the active oxidase (Fig. 10). HMGB1/TLR-4 signaling in the setting of hemorrhagic shock/resuscitation (HS/R) induces neutrophil NADPH oxidase activation. HS/R primes circulating neutrophils (PMN) NADPH oxidase activation in wild-type mice. This induction is diminished in TLR-4-mutant C3H/HeJ mice. Neutralizing Ab to HMGB1 prevents HS/R-induced activation of PMN NADPH oxidase. In addition, *in vitro* stimulation of PMN with recombinant HMGB1 causes TLR-4-dependent activation of NADPH oxidase as well as increased ROS production through both myeloid differentiation factor 88 (MyD88)-interleukin-1 receptor-associated kinase 4 (IRAK4)-p38 MAPK and MyD88-IRAK4-Akt signaling pathways (55). Thus p38 MAPK and Akt, as downstream components of HMGB1-TLR-4-MyD88-IRAK4 signaling, may act in a coordinate manner. Recent studies indicate that TLR-4-HMGB1 axis involves in the inflammatory basis of two very common disease processes, skin cancer and epilepsy (138, 148). However, whether or not oxidative stress involving in these processes remains to be elucidated.

Redox of HMGB1 and DCs

The mammalian immune system discriminates between modes of cell death. Necrosis often results in inflammation and adaptive immunity, whereas apoptosis tends to be anti-inflammatory and promote immune tolerance. DCs are key components of innate and adaptive immune responses. The HMGB1 protein induces the migration and activation of human DCs (147, 255), and NK-DC cross-talk (141, 144). However, HMGB1 produced by colon cancer cells suppresses nodal DCs to promote anticancer immunity (111). HMGB1 interacts with TLR-4 on DCs, which are selectively involved in the cross-priming of antitumor T lymphocytes *in vivo* (7). NK cells trigger immature DCs to polarize and secrete IL-18. In turn, DCs activate NK cells that secrete HMGB1, and in turn induce DC maturation and promote DC survival (196).

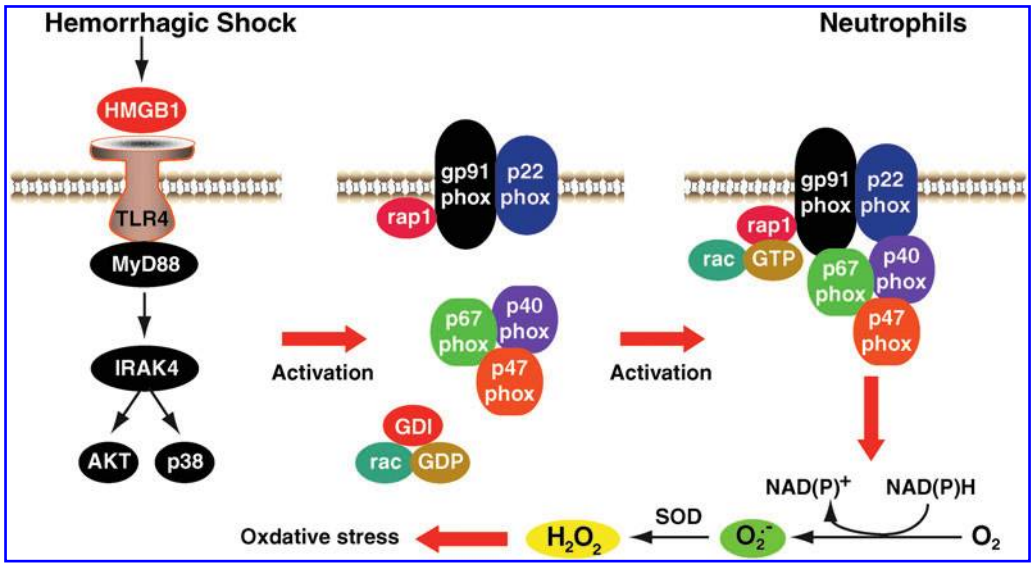

FIG. 10. TLR-4 mediates HMGB1-induced reactive oxygen species (ROS) production. The integral membrane of the phagocyte consists of two subunits: p22phox and gp91phox, which, respectively, produce the smaller and larger chain of the cytochrome-b558. Two cytosolic subunits (p67phox and p47phox), a p40phox accessory protein, and an Rac-GTP binding protein then translocate to the cell membrane upon cell activation to form the NADPH oxidase complex, which generates a respiratory burst. Hemorrhagic shock/resuscitation-induced HMGB1 release. HMGB1 increases neutrophil NADPH oxidase activation and subsequent ROS production by TLR-4-MyD88-IRAK4 signaling. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

Moreover, RAGE and HMGB1 play a nonredundant role in DC homing to lymph nodes (135). HMGB1 and RAGE are required for the maturation of human plasmacytoid DCs (47). However, HMGB1 suppresses plasmacytoid DC cytokine secretion and maturation in response to TLR-9 agonists, including the hypomethylated oligodeoxynucleotide CpG- and DNA-containing viruses (165). Thus, HMGB1 coming from necrotic cells is an important activator of DCs (Fig. 11).

Initially, it was believed that the release of HMGB1 from the nucleus either to the cytosol or to the extracellular space was sufficient to distinguish necrotic from apoptotic cells (190). However, this idea has recently come into question for several reasons. First, nuclear DNA and associated proteins are released in a time-dependent manner during apoptosis (32) and that the binding of HMGB1 to DNA is increased during apoptosis, consistent with the notion that late-stage apoptotic cells can release both DNA and HMGB1 (15). In addition, apoptotic tumor cells release HMGB1 (15, 227). It was, therefore, postulated that a post-translational modification of HMGB1 is responsible for its various activities (18, 164, 236). Caspase activation targeted the mitochondria to produce ROS, which are critical to tolerance induction by apoptotic cells. Notably, ROS oxidized HMGB1 released from dying cells and thereby neutralized its stimulatory activity (100). Apoptotic cells failed to induce tolerance and instead stimulated immune responses by scavenging or by mutating a mitochondrial caspase target mitochondrial complex 1 protein p75 NDUFS1 when ROS activity was prohibited. Similarly, the oxidation of HMGB1 Cys106 alone was sufficient to block the immunogenic activity of HMGB1 for DCs (Fig. 11). Thus, although ROS are often associated with inflammatory conditions, other stimuli that are present in such settings are likely to override the effects on HMGB1 to promote immunity over tolerance during inflammation (100).

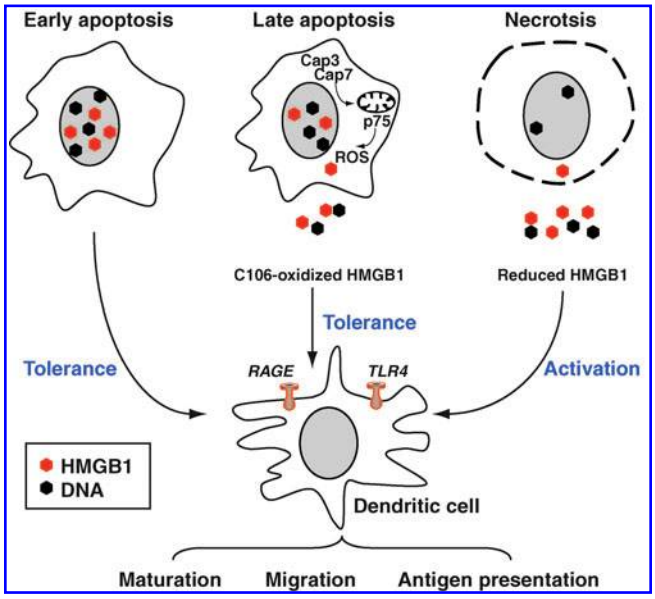

FIG. 11. Redox of HMGB1 mediated its immunogenic activity. In necrotic cells, HMGB1 is released from dying cells possessing full immunogenic activity, including dendritic cell (DC). Binding of HMGB1 to RAGE and/or TLRs induces activation and/or maturation of DCs. In contrast, in cells undergoing apoptosis, activated caspase-3 and caspase-7 cleave the complex I component p75 NDUFS1 and thus halt the respiratory chain, leading to production of ROS, which oxidize cysteine 106 in HMGB1. Oxidized HMGB1 cannot fully activate DCs and has tolerogenic activities. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

HMGB1 and Ischemia Reperfusion Injury

Ischemia reperfusion (I/R) injury is a pathophysiologic process whereby hypoxic organ damage is accentuated after return of blood flow and oxygen delivery. The absence of oxygen and nutrients from blood creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function. Transient episodes of ischemia are encountered during solid organ transplantation, trauma, hypovolemic shock, and elective liver resection, when inflow occlusion or total vascular exclusion is used to minimize blood loss. HMGB1 levels were increased during mice liver I/R as early as 1 h after reperfusion and then increased in a time-dependent manner up to 24 h (232). Inhibition of HMGB1 activity with neutralizing antibody significantly decreased liver damage after I/R, whereas administration of recombinant HMGB1 worsened I/R injury. Moreover, HMGB1 is an early mediator of injury and inflammation in liver I/R (245) and kidney I/R (33, 252) and implicates TLR-4 (109, 232, 252), TLR-9 (10), RAGE (270) as receptors that is involved in the process.

HMGB1 is a marker of injury in human liver and kidney transplantation (80, 109, 267). Further, HMGB1 release induced by liver ischemia involves TLR-4-dependent ROS production and calcium-mediated signaling (231). HMGB1 release induced by oxidative stress was markedly reduced by inhibition of calcium/calmodulin-dependent kinases (231). Inhibition of HMGB1 activity by injection of neutralizing antibody partially abolished the increase in liver manganese SOD, a key mitochondrial antioxidant enzyme, after I/R (160). Pretreatment of mice with HMGB1 significantly decreased liver damage after I/R (85). The protection observed in mice pretreated with HMGB1 was associated with higher expression of IL-1R-associated kinase-M, a negative regulator of TLR-4 signaling, compared with controls (85). Moreover, HMGB1-TLR-4 pathway also plays an important role in the initiation of systemic inflammation and end-organ injury after isolated peripheral tissue injury (114). In the heart, HMGB1 plays a major role in the early events after I/R injury by binding to RAGE, resulting in the activation of proinflammatory pathways and enhanced myocardial I/R injury (5, 154). Src family kinases are necessary for cell migration induced by HMGB1-RAGE pathway (157). However, TLR-4 mediates inflammation signaling after cold I/R in the heart (92). HMGB1 is released and plays a cytokine-like function in the postischemic brain (72, 105) and ischemic injury from neurons (170). HMGB1 promotes metalloproteinase-9 upregulation through TLR-4 after cerebral ischemia (171). Moreover, HMBG1 mediates cerebral I/R injury by TIR-domain-containing adapter-inducing interferon-β (TRIF)-independent TLR-4 signaling (258). In rats, treatment with neutralizing anti-HMGB1 monoclonal antibody remarkably ameliorated brain infarction (114). Cannabidiol prevents a postischemic injury progressively induced by cerebral ischemia *via* a HMGB1-inhibiting mechanism (72). Taken together, HMGB1 is central to early activation of the innate immune response in the setting of organ I/R (Fig. 12).

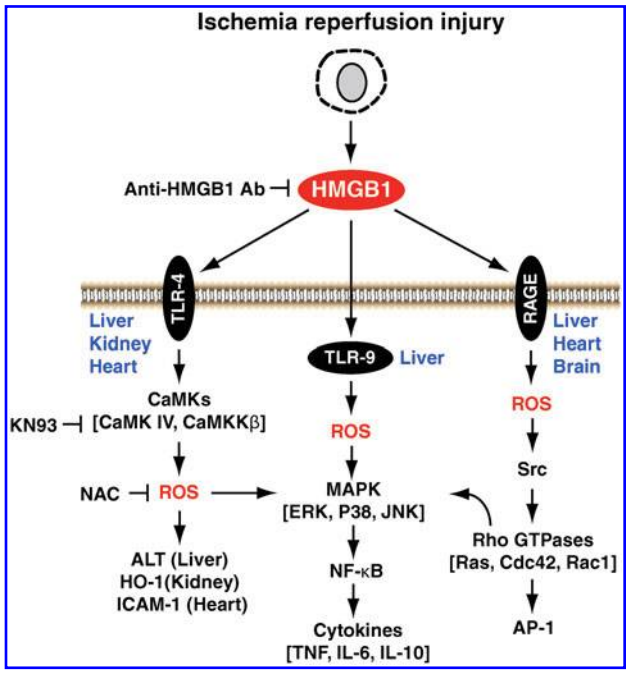

FIG. 12. Signaling pathway of HMGB1-mediated ischemia reperfusion injury. HMGB1 is an early mediator of injury and inflammation in liver, kidney, heart, and brain ischemia reperfusion injury and implicates TLR-4, TLR-9, and RAGE as receptors that are involved in the process. HMGB1's extracellular function partly through activation of MAPKs and NF-κB pathway. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

HMGB1 and Atherosclerosis

Atherosclerosis is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. Atherosclerosis develops from low-density lipoprotein (LDL) molecules becoming oxidized (LDL-ox) by free radicals, particularly ROS. When LDL-ox comes in contact with an artery wall, a series of reactions occur to repair the damage to the artery wall caused by LDL-ox (22, 194, 240). Endothelial dysfunction is a key triggering event in atherosclerosis. HMGB1 activates vascular endothelial cells to express and the secretion of intercellular adhesion molecule 1, vascular cell adhesion molecule 1, RAGE, TNF-α, IL-8, monocyte chemotactic protein-1, plasminogen activator inhibitor 1, and tissue plasminogen activator (Fig. 13) (118, 230). Hyperglycemia-induced ROS production increases expression of RAGE and HMGB1 in human endothelial cells (259). Increased expression of the HMGB1 is observed in human atherosclerotic lesions (82, 93). Activated vascular smooth muscle cells are the source of HMGB1 in human advanced atherosclerotic lesions (82). HMGB1 directly stimulates the production of both C-reactive protein and matrix metalloproteinase through RAGE (82). Moreover, HMGB1 promotes smooth muscle cells in human atherosclerotic plaques to secrete a variety of vasoactive substances and to proliferate (166). HMGB1 induces phospholipase A2 and prostaglandin E2 production, which is the lipid mediators observed during atherogenesis (88). Simvastatin can alleviate the formation of the atherosclerotic plaques in the atherosclerotic rats, and decrease the protein and mRNA expression of HMGB1 (262). In a mouse model of atherosclerosis, apoE$^{-/-}$ mice, vascular and inflammatory stresses mediate atherosclerosis *via* RAGE and HMGB1 (69). Although diabetic apoE$^{-/-}$ mice have accelerated plaque accumulation, diabetic RAGE$^{-/-}$apoE$^{-/-}$

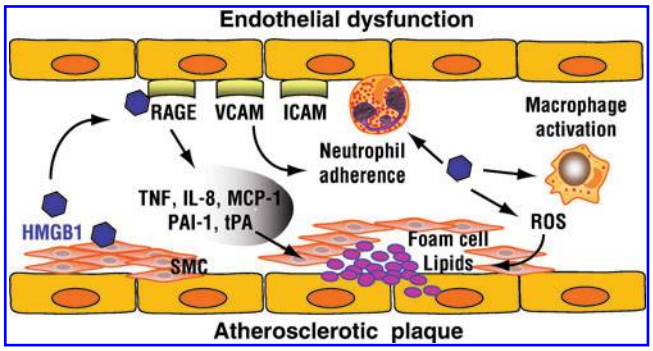

FIG. 13. HMGB1 induces endothelial dysfunction and promotes atherosclerotic plaque formation. Activated vascular smooth muscle cells (SMCs) are the source of HMGB1 in human advanced atherosclerotic lesions. HMGB1 activates vascular endothelial cells to express and the secretion of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), RAGE, TNF-α, IL-8, monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor 1 (PAI-1), and tissue plasminogen activator (tPA). Moreover, HMGB1 activates macrophagy, promotes neutrophil adherence, and increases ROS production. Atherosclerosis develops from low-density lipoprotein (LDL) molecules becoming oxidized by ROS in artery wall. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

mice had significantly reduced atherosclerotic plaque area to levels not significantly different from control apoE$^{-/-}$ mice (203). These beneficial effects on the vasculature were associated with attenuation of leukocyte recruitment and decreased expression of proinflammatory mediators, including the NF-κB subunit p65, vascular cell adhesion molecule 1, and monocyte chemotactic protein-1. Reduced oxidative stress, as reflected by staining for nitrotyrosine and reduced expression of various NADPH oxidase subunits, gp91phox, p47phox, and rac-1, is also noted. Both RAGE and RAGE ligands, including S100A8/A9, HMGB1, and the AGE carboxymethyllysine, are increased in plaques from diabetic apoE$^{-/-}$ mice. Further, the accumulation of AGEs, HMGB1, and other ligands for RAGE is reduced in diabetic RAGE$^{-/-}$apoE$^{-/-}$ mice (203). Thus, RAGE and its ligand deficiency attenuate the development of atherosclerosis. Recent study shows that HMGB1 induced vascular endothelial activation by TLR-4/NF-κB signaling pathway (257).

HMGB1 and Aging

Aging is an inherently complex process that is manifested within an organism at genetic, molecular, cellular, tissue, and systemic levels. Aging is a major risk factor for several common neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and Hunting's disease (Fig. 14). Although the fundamental mechanisms are still poorly understood, a growing body of evidence points toward ROS as one of the primary determinants of aging (58, 108). Reduction of nuclear HMGB1 protein level within the nucleus is associated with DNA double-strand break (DDSB)-mediated neuronal damage in Huntington's disease (168). HMGB1 is localized in the nuclei of neurons and astrocytes in mouse, and the protein level changes in various brain regions age dependently (53). HMGB1 reduction is noted in neurons

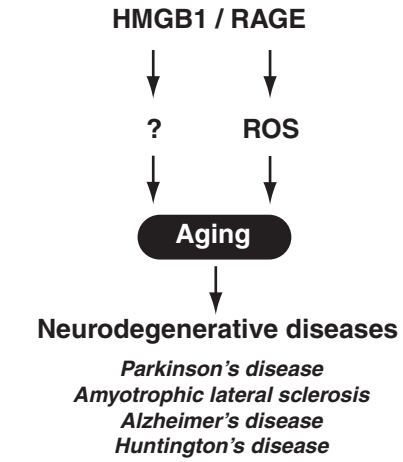

FIG. 14. The HMGB1/RAGE pathway is involving in aging. Aging is a major risk factor for several common neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease. ROS is one of the primary determinants of aging.

during aging, whereas it increases in astrocytes. In contrast, DDSB remarkably accumulates in neurons, but it does not change significantly in astrocytes during aging. These findings indicate that HMGB1 expression during aging is differentially regulated between neurons and astrocytes, and suggest that the reduction of nuclear HMGB1 might be causative for DDSB in neurons of the aged brain (53). HMGB1 binds preferentially to aggregated alpha-synuclein and is present in alpha-synuclein filament-containing Lewy bodies isolated from brain tissue affected with dementia or Parkinson's disease (124). Amyloid-β peptide is central to the pathology of Alzheimer's disease. It is neurotoxic, directly by inducing oxidant stress and indirectly by activating microglia. Increased expression of RAGE in Alzheimer's disease brain mediates the pathogenesis of neuronal dysfunction and death (253). sRAGE levels are significantly decreased in the serum of the patients with amyotrophic lateral sclerosis (81).

Potential Antioxidant Therapy Targeting HMGB1 Release

Several agents such as ethyl pyruvate, quercetin, green tea, N-acetylcysteine (NAC), and curcumin have not only antioxidative properties, but also antiinflammatory properties. They are protective in the setting of experimental inflammation, partly through attenuating systemic HMGB1 accumulation (Fig. 15).

Ethyl pyruvate

Ethyl pyruvate ($CH_3COCOOC_2H_5$) is a simple derivative in Ca^{2+}- and K^+-containing balanced salt solutions of pyruvate originally designed to avoid the problems associated with the instability of pyruvate in solution. Treatment with ethyl pyruvate has been shown to improve survival and ameliorate organ dysfunction in a wide variety of preclinical models of critical illnesses, such as severe sepsis, acute respiratory distress syndrome, burn injury, acute pancreatitis, and stroke (56, 57). It ameliorates the effects of I/R injury

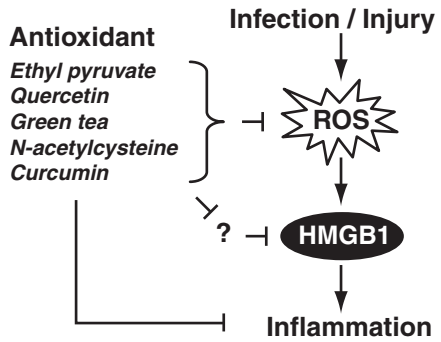

FIG. 15. Several agents such as ethyl pyruvate, quercetin, green tea, N-acetylcysteine, and curcumin have not only antioxidative properties, but also antiinflammatory properties. They are protective in the setting of experimental inflammation, partly through attenuating systemic HMGB1 accumulation.

in many organs (33, 98, 244, 265). Ethyl pyruvate is also an effective scavenger of oxygen radicals (39, 104, 237). Ethyl pyruvate was also found to be a pharmacological inhibitor of HMGB1 secretion (234). Ethyl pyruvate inhibits the release of TNF-α and HMGB1 from endotoxin-stimulated RAW 264.7 murine macrophages, as well as attenuates activation of both the p38 MAPKs and NF-κB signaling pathways. Ethyl pyruvate treatment of septic mice decreases circulating levels of HMGB1 (234). Pretreatment with ethyl pyruvate also prevents endotoxin lethality and inhibits the release of TNF-α and HMGB1 (234). Ethyl pyruvate decreases HMGB1 release and ameliorates murine colitis (40) and renal ischemia and reperfusion injury (33). Serum IL-6 and HMGB1 levels, which are elevated after tumor injection, are decreased significantly in ethyl pyruvate-treated animals (120).

Quercetin

As an antioxidant, quercetin (3,3′,4′,5,7-pentahydroxyflavone dehydrate, $C_{15}H_{10}O_7$) has anti-inflammatory effects, regulating NO, IL-6, and TNF-α release (44, 136), thereby alleviating oxidative damage in the tissue (1, 44), and inhibiting the LPS-induced delay in spontaneous apoptosis and activation of neutrophils (126). Quercetin treatment significantly reduces circulating levels of HMGB1 in animals with established endotoxemia (218). In macrophage cultures, quercetin inhibits release as well as the cytokine activities of HMGB1, including limiting the activation of MAPKs and NF-κB, two signaling pathways that are critical for HMGB1-induced subsequent cytokine release. Quercetin and the autophagic inhibitor wortmannin inhibit LPS-induced type II microtubule-associated protein 1 light chain 3 production and aggregation as well as HMGB1 translocation and release (218).

Green tea

Green tea contains potent antioxidants called catechins. Tea extracts increase antioxidant activity in the blood (74). Accounting for 50% to 80% of the total catechin, epigallocatechin gallate (EGCG, $C_{22}H_{18}O_{11}$) is effective in attenuating endotoxin-induced HMGB1 release by macrophage and monocytes (117). In addition, EGCG dose dependently inhibited HMGB1-induced release of TNF-A, IL-6, and NO in macrophage cultures (123). EGCG completely abrogated accumulation/clustering of exogenous HMGB1 on the macrophage cell surface (117), suggesting that EGCG inhibits HMGB1 cytokine activities by preventing its cell surface accumulation/clustering. Consistently, delayed administration of EGCG significantly attenuated circulating levels of HMGB1, as well as surrogate markers of experimental sepsis (such as IL-6) (117). Considered together, these experimental data indicate that EGCG protects mice after otherwise lethal sepsis partly by attenuating systemic HMGB1 accumulation and partly by inhibiting the HMGB1-mediated inflammatory response.

N-acetylcysteine

NAC, $HSCH_2CH(NHCOCH_3)CO_2H$, is a potent antioxidant that has been used to investigate the role of ROS in numerous biological and pathological processes (268). NAC decreases the expression of TNF-α, IL-1, IL-6, IL-12p40, and MIP-1α in the setting of endotoxin-induced lung inflammation (178). NAC has the potential to counter the intertwined redox and inflammatory imbalances in cystic fibrosis (228). *In vitro*, NAC inhibited hypoxia- or H_2O_2-mediated HMGB1 release in hepatocytes (231). NAC reduces I/R liver injury in wild-type mice to the level observed in TLR-4 mutant mice but fails to reduce the injury in TLR-4 mutant mice. *In vivo*, NAC treatment inhibits the expression of TNF-α and IL-6 mRNA, and serum HMGB1 levels after I/R liver injury (231). These results indicate that HMGB1 release during I/R is mediated, in part, by TLR-4 signaling and parallels the extent of oxidant production.

Curcumin

Curcumin ($[HOC_6H_3(OCH_3)CH=CHCO]_2CH_2$) is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family. Curcumin acts as a free radical scavenger and antioxidant, inhibiting lipid peroxidation and oxidative DNA damage (200). Curcumin inhibited PMA-mediated activation of ERK and NF-κB transcriptional activity (121). In rats, curcumin decreased oxidative stress, inhibited NF-κB activation, and ameliorated liver pathologic changes in the setting of ethanol-induced liver injury (186). Uric acid, a final metabolite of purine metabolism in mammals but not birds, triggers the release of HMGB1 in a time- and dose-dependant fashion in mouse macrophage cells (RAW 264.7), human leukemic promonocytes (THP-1 cells), as well as in macrophages, but not in fibroblasts obtained from synovial fluid of patients with rheumatoid arthritis. Curcumin significantly suppressed HMGB1 release in response to uric acid (19).

Conclusion

ROS intermediates are indeed signaling molecules in various pathways regulating both cell survival and cell death. HMGB1 is both a nuclear factor and a secreted protein. In the cell nucleus it acts as a DNA chaperone. Outside the cell, it serves as a DAMP signal. The findings discussed here support the notion that HMGB1 is integral to the response to oxidative stress. The precise mechanisms promoting the release of HMGB1 in the setting of oxidative stress and the signaling pathways it activates remain to be completely elucidated. Understanding HMGB1 and its complex effects in the setting of oxidative stress may lead to the development of novel strategies to attenuate oxidative injury in various clinical

states, particularly those associated with chronic inflammation, including cancer.

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Address correspondence to:
Dr. Daolin Tang
The DAMP Laboratory
Department of Surgery
G.21 Hillman Cancer Center
Pittsburgh, PA 15213

E-mail: tangd2@upmc.edu

Prof. Michael T. Lotze
The DAMP Laboratory
Department of Surgery
G.27A Hillman Cancer Center
Pittsburgh, PA 15213

E-mail: lotzemt@upmc.edu

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Abbreviations Used

AA = amino acid
AGE = advanced glycation end product
APE1 = apurinic/apyrimidinic endonuclease 1/redox factor-1
ATG = autophagy-related gene
CMA = chaperone-mediated autophagy
CRM1 = chromosome region maintenance 1
Cys = cysteines
Cyt c = cytochrome c
DAMP = damage-associated molecular pattern molecule
DCs = dendritic cells
DDSB = DNA double-strand break
EGCG = epigallocatechin gallate
ER = endoplasmic reticulum
ERK = extracellular signal-regulated kinase
HDAC1 = histone deacetylase-1
HMGB1 = high-mobility group box 1 protein
H_2O_2 = hydrogen peroxide
HSP = heat shock protein
HS/R = hemorrhagic shock/resuscitation
ICAM-1 = intercellular adhesion molecule 1
IL = interleukin
I/R = ischemia reperfusion
IRAK4 = interleukin-1 receptor-associated kinase 4
LAMP-2A = lysosome-associated membrane protein type-2A
LDL = low-density lipoprotein
LDL-ox = oxidized low-density lipoprotein
LPS = lipopolysaccharide
MAPKs = mitogen-activated protein kinases
MCP-1 = monocyte chemotactic protein-1
METC = mitochondrial electron transport chain
MPT = mitochondrial permeability transition
MyD88 = myeloid differentiation factor 88
NAC = N-acetylcysteine
NADPH = nicotinamide adenine dinucleotide phosphate
NF-κB = nuclear factor-κB
Nix = nip3-like protein X
NK = natural killer
NO = nitric oxide
$O_2^{\bullet -}$ = superoxide anion
$^1O_2$ = singlet oxygen
$^{\bullet}OH$ = hydroxyl radical
ONOO• = peroxynitrite
PAI-1 = plasminogen activator inhibitor 1
PKC = protein kinase C
PMN = primes circulating neutrophils
PTKs = tyrosine kinases
PTPs = protein tyrosine phosphatases
PUMA = p53-upregulated mediator of apoptosis
RAGE = receptor for advanced glycation end products
ROS = reactive oxygen species
R-SNO = S-nitrosothiol
R-SOH = sulphenic acid
R-S-S-R = disulphide
-SH = thiol side-chain
SMC = smooth muscle cells
SOD = superoxide dismutase
TLR = Toll-like receptor
TNF = tumor necrosis factor
tPA = tissue plasminogen activator
TREM-1 = triggering receptor expressed on myeloid cells-1
TRIF = TIR-domain-containing adapter-inducing interferon-β
Trx1 = thiol-disulfide oxidoreductase thioredoxin-1
VCAM-1 = vascular cell adhesion molecule 1

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