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High-Mobility Group Box 1 and Autophagy

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<http://dx.doi.org/10.5772/63476>

Abstract

High-mobility group box 1 (HMGB1) is an architectural chromosomal protein and stress sensor that plays a critical role in various physiological and pathological processes, including cell death and survival. Autophagy is the major pathway involved in the degradation of proteins and organelles, maintenance of cellular homeostasis, and promotion of survival during environmental stress. HMGB1 plays an important location-dependent role in the regulation of autophagy. Nuclear HMGB1 contributes to mitophagy by regulation of heat shock protein beta-1 (HSPB1) expression and cytoskeleton dynamics. Cytoplasmic HMGB1 is a novel coiled-coil myosin-like BCL2-interacting protein (BECN1)-binding protein in the induction of autophagosome formation. Extracellular-reduced HMGB1 triggers autophagy in an advanced glycosylation end product-specific receptor (AGER)-dependent manner. HMGB1-dependent autophagy promotes chemotherapy resistance, sustains the tumor metabolism requirement and T-cell survival, prevents polyglutamine aggregates and excitotoxicity, and protects against endotoxemia, bacterial infection, and ischemia-reperfusion injury in vitro or in animal studies. Targeting the HMGB1-mediated autophagy pathway may be required to address whether or not this approach is therapeutically advantageous in human disease.

Keywords: HMGB1, autophagy, ATG, disease, pathway

1. Introduction

The autophagic network is complex and requires a core regulator: autophagy-related genes/proteins (ATGs) [1]. The study of the molecular basis of autophagy started with the discovery of Aut1 (now Atg3) [2], Apg13 (now Atg13) [3], and Apg1 (now Atg1; the mammalian homolog is ULK1 [unc-51 like autophagy-activating kinase 1]) [4] in *Saccharomyces cerevisiae* in 1997. Currently, over 38 ATGs that control membrane dynamics during

autophagy have been identified in the cells of different organisms, ranging from yeasts to mammals [5–7].

In addition to ATGs, several non-ATG proteins are involved in the regulation of autophagy through direct or indirect interplay with ATGs. High-mobility group protein 1 (HMGB1) belongs to the family of the high-mobility group (HMG) nuclear proteins [8]. Here, we highlight the emerging role of HMGB1 as an important non-ATG protein in the regulation of autophagy.

2. HMGB1 structure

HMGB1 is a highly conserved protein and present in almost all cell types [9]. The genetic sequence of human HMGB1 is located on chromosome 13q12–13 and the protein sequence of human HMGB1 is composed of 215 amino acids (AAs). Human HMGB1 is 99% AA identical to mouse, rat, bovine, and porcine HMGB1. HMGB1 structurally consists of three different domains: two DNA-binding domains (HMG boxes A and B) and a negatively charged 30 AA C-terminal region that contains only Asp and Glu. Both the HMGB1 A and B boxes are about 75–80 AAs long and are formed by two short and one long α -helixes that upon folding, produce an L- or V-shaped three-dimensional domain structure [10–12]. The cytokine activity of HBMG1 is restricted to the HMG B box because AA89–108 of HMGB1 can be recognized by Toll-like receptor (TLR)-4 to induce the release of proinflammatory cytokines [13]. In contrast, the purified recombinant A box has been identified as an antagonistic and anti-inflammatory factor [14]. AA150–183 of HMGB1 is responsible for binding to the receptor for advanced glycation end products (AGER/RAGE) to induce cell migration [15]. In addition, to mediate cell migration, AGER is also important for HMGB1-induced autophagy [16], metabolism [17], and inflammation [18] in a context-dependent manner. AA 27–43 and 178–184 of HMGB1 contain two nuclear localization signals, respectively. Acetylation of nuclear localization signals triggers HMGB1 translocation from the nucleus to the cytosol. HMGB1 is a redox protein and contains three cysteines (C23, C45, and C106). C23 and C45 form an intramolecular disulfide bond within the A-domain, while C106 is redox inactive and remains reduced [19, 20]. In general, reduced HMGB1 exhibits immune activity, whereas oxidized HMGB1 displays immune tolerance [21, 22]. In addition to regulating activity, redox also affects HMGB1 translocation and release [23, 24]. For example, mutant C106 can cause HMGB1 translocation from the nucleus to the cytosol. Indeed, oxidative stress plays a central role in mediating active HMGB1 secretion as well as passive release [25]. Inhibition of HMGB1 release by antioxidant compounds such as *N*-acetyl-cysteine [26], quercetin [27], edaravone [28], epigallocatechin gallate [29], and resveratrol [30] improves animal survival and limits the inflammatory response in infection and tissue damage.

3. HMGB1 function

Under normal conditions, over 95% of intracellular HMGB1 is located in the nucleus and functions as a deoxyribonucleic acid (DNA) chaperone. Under stress conditions, HMGB1 can be released from the intracellular to the extracellular space [31]. Extracellular HMGB1 acts as a damage-associated molecular pattern molecule (DAMP) to mediate the inflammation, immunity, and metabolism responses in human disease [9, 32]. Thus, the function of HMGB1 depends on its location. Below, we summarize the major functions of nuclear, cytosolic, and extracellular HMGB1, respectively.

3.1. Nuclear HMGB1

Like the histones, HMGB1 is among the most important chromatin proteins. In particular, the DNA-binding domains confers HMGB1 the ability to recognize, bind, and bend different DNA structures such as DNA mini-circles, four-way junctions, looped structures, hemicatenated DNA, and triplex DNA [33]. This DNA chaperone activity is critical for HMGB1-mediated nuclear homeostasis and genome stability.

3.1.1. Nucleosome dynamics and quantity

The nucleosome is the fundamental subunit of chromatin. Each nucleosome is composed of a core particle, DNA, and a linker protein. The proteins in the core particle and linker proteins are called histones. HMGB1 can bind to histones and DNA to promote nucleosome sliding, relax nucleosome structure, and make chromatin more accessible [34, 35]. Loss of HMGB1 leads to the loss and release of nucleosomes [36, 37]. Extracellular nucleosomes, including histones and DNA, are inflammatory mediators in cancer, sepsis, and pancreatitis [38].

3.1.2. Gene transcription

HMGB1 knockout mice die shortly after birth due to hypoglycemia and exhibit a defect in the transcriptional enhancement of the glucocorticoid receptor [39]. In addition to the glucocorticoid receptor, HMGB1 interacts with a number of transcription factors (e.g., p53, p73, the retinoblastoma protein, nuclear factor kappa B [NF- κ B], and estrogen receptor) to either activate or repress the transcription of specific genes.

3.1.3. DNA repair

The major forms of DNA damage include single-strand breaks, double-strand breaks, alteration of bases, hydrolytic depurination, hydrolytic deamination of cytosine and 5-methylcytosine bases, formation of covalent adducts with DNA, and oxidative damage to bases and to the phosphodiester backbone of DNA. Loss of HMGB1 increases these lesions [40, 41] and nuclear HMGB1 contributes to base excision repair, nucleotide excision repair, and mismatch repair [33].

3.1.4. *V(D)J recombination*

VDJ recombination is the process by which T cells and B cells randomly assemble different gene segments—known as variable (V), diversity (D), and joining (J) genes—in order to generate unique receptors (known as antigen receptors) that can collectively recognize many different types of molecules. HMG proteins, including HMGB1, are important components of the V(D)J recombinase complex [42].

3.1.5. *Telomere homeostasis*

Telomeres are caps with a region of repetitive nucleotide sequences at the end of chromosomes. Telomerase is an enzyme made of protein and ribonucleic acid (RNA) subunits that elongates chromosomes by adding TTAGGG sequences to the end of existing chromosomes. Telomere shortening is involved in the aging process. Loss of HMGB1 reduces telomerase activity, decreases telomere length, and increases chromosomal stability on a cellular level [43, 44].

3.2. Cytosolic HMGB1

Early studies have shown that the expression of HMGB1 in hepatic and brain tissues is high; it has been suggested a functional role of HMGB1 in both the nucleus and the cytoplasm [45, 46]. Recent studies have demonstrated that various tissues have a near-universal high expression of HMGB1. Cytoplasmic localization of HMGB1 has been observed in living fibroblasts [47], thymocytes [48], and several different tissues (e.g., liver, kidney, heart, and lung) [49]. Normally, the nuclear-to-cytoplasmic HMGB1 ratio is about 30:1 and this ratio is significantly reduced in cellular stress [49]. HMGB1 translocates from the nucleus to the cytoplasm, including the mitochondria and lysosomes, following various types of stressors such as inflammatory cytokines/chemokines and thermal and hypoxic stress. Although the study of the function of cytosolic HMGB1 remains poor, our research indicates that the main function of HMGB1 in the cytoplasm is to function as a positive regulator of autophagy and mitophagy (discussed later at section 4.2).

3.3. Extracellular HMGB1

HMGB1 can be actively secreted by immune cells or passively released by dead, dying, or injured cells [50]. Extracellular HMGB1 has multiple functions and is involved in several processes.

3.3.1. *Cell differentiation*

The first reported activity of extracellular HMGB1 is that HMGB1 promotes murine erythroleukemia cell differentiation [51, 52]. Structurally, the N-terminal region of HMGB1 is responsible for promoting murine erythroleukemia cell differentiation [53]. In addition to murine erythroleukemia cells, extracellular HMGB1 triggers the differentiation of chronic lymphocytic leukemia, stem cells, dendritic cells (DCs), and T cells [54, 55].

3.3.2. *Inflammation and immunity*

HMGB1 is an important late mediator released by macrophages in sepsis [31]. In addition to macrophages, many immune cells (e.g., neutrophils, mast cells, eosinophils, DCs, T cells, and natural killer cells) can release HMGB1 in response to infection [56]. HMGB1 cannot be actively secreted via the classical endoplasmic reticulum -Golgi secretory pathway due to lacking a leader signal sequence [57]. In turn, secretory lysosome contributes to HMGB1 secretion [58]. This process is regulated by metabolism [59]. Once released, HMGB1 can activate immune cells to sustain the inflammatory response. This process is regulated by redox status, receptor, and partner of HMGB1. For example, HMGB1 can bind and activate different signaling transduction cell receptors such as AGER, TLRs (e.g., TLR-2, -4, and -9), CD24, and TIM3 [60–62]. HMGB1 is very “sticky” and can bind to various extracellular pathogen-associated molecular patterns (PAMPs) (e.g., lipopolysaccharide) and DAMPs (e.g., DNA and histones) to amplify inflammatory and immune responses [60, 63].

3.3.3. *Cell migration*

HMGB1 has chemokine activity to induce cell invasion and migration, a key process during the development of most organisms [64]. The potential mechanism includes HMGB1-mediated signaling transduction (e.g., ERK [65, 66] and Cdc42 [67]), transcriptional factor activation (e.g., NF- κ B), and chemokine production.

3.3.4. *Tissue regeneration*

Tissue regeneration is the body’s autohealing reaction once it gets injured or damaged. HMGB1 can stimulate myocardial regeneration, which may facilitate cardiac repair [68–71], cardiomyocyte hypertrophy [72], or cardiac fibrosis [73].

3.3.5. *Angiogenesis*

Angiogenesis is the growth of blood vessels from the existing vasculature. Treatment with HMGB1 protein increases angiogenesis by the secretion of vascular endothelial growth factor, an important inducer of angiogenesis [74].

4. HMGB1 and autophagy

4.1. Nuclear HMGB1 in autophagy

Mitophagy is an important mitochondrial quality control mechanism to sustain mitochondrial structure and function. We recently demonstrated that the nuclear protein HMGB1 modulates mitochondrial respiration and morphology by sustaining mitophagy through the regulation of heat shock protein β -1 (HSPB1) gene expression [75]. Metabolic activities in normal cells rely primarily on mitochondrial oxidative phosphorylation (OXPHOS) to generate adenosine triphosphate (ATP) for energy. In contrast, cancer cells mainly use glycolysis to generate ATP

for energy. This type of energy reprogramming is called the Warburg effect. Interestingly, knockout or knockdown of HMGB1 or HSPB1 significantly inhibits OXPHOS and glycolysis in cancer cells or fibroblasts [75]. As expected, ATP production is decreased in HMGB1- or HSPB1-deficient cells. HSPB1 is a member of the small heat shock proteins (HSPs), which are important for protein folding [75]. HSPB1, but not other HSPs, is significantly inhibited in HMGB1-/-cells. Transfection of HMGB1 complementary DNA (cDNA) into HMGB1 cells restores HSPB1 expression at messenger RNA (mRNA) and protein levels. This process is not dependent on heat shock factor 1 (HSF1), the major transcription factor for HSP expression. Importantly, forced expression of HSPB1 by gene transfection corrects the deficiency in mitochondrial respiration, ATP production, and mitochondrial fragmentation, which is observed in HMGB1-deficient cells [75]. Thus, HSPB1 is the primary downstream mediator of HMGB1's effect on the regulation of mitochondrial homeostasis.

Alterations to the cytoskeleton during cell death and autophagy have been described in a variety of different cells. Previous studies have suggested that HSPB1 has a direct influence on the dynamics of cytoskeletal elements by HSPB1 phosphorylation [76, 77]. Similarly, by using cytoskeleton inhibitor cytochalasin D, loss of HSPB1 or mutation of its phosphorylation sites at serines 15 and 86 decreases starvation and rotenone-induced autophagy and mitophagy and impairs autophagosome and lysosome fusion [75]. These findings suggest that impaired cytoskeleton is involved in HMGB1-HSPB1 pathway-mediated mitophagy.

PTEN-induced putative kinase-1 (PINK1) is a kinase of the outer mitochondrial membrane, and PARK2 is a protein implicated in autosomal recessive juvenile Parkinsonism. The PINK1-PARK2 pathway has been largely implicated in the removal of damaged mitochondria with depolarized membranes in mammalian cells [78]. Upon mitochondrial membrane depolarization, PINK1 mediates the stress-induced mitochondrial translocation of PARK2. Subsequently, mitochondrial PARK2 drives the formation of Lys27-linked ubiquitin chains on the outer membrane of voltage-dependent anion channel 1 (VDAC1) [78]. These chains are then recognized by the autophagic adapter protein sequestosome 1 (SQSTM1/p62). SQSTM1 binds directly to LC3 to facilitate the formation of autophagosomes engulfing damaged mitochondria. HMGB1 and HSPB1 regulate PARK2 translocation and VDAC1 ubiquitination during mitochondrial depolarization. Knockdown of PINK1 or PARK2 abolishes the HSPB1-induced restoration in ATP production and reduction in mitochondrial fragmentation in HMGB1-deficient cells. Collectively, activation of the PINK1-PARK2 pathway is required for the HMGB1-HSPB1-dependent autophagic clearance of mitochondria. HMGB1 and HSPB1 translocate into the mitochondria during cellular stress. Whether these proteins interact directly with PINK1 or PARK2 remains unknown.

4.2. Cytosolic HMGB1 in autophagy

Release of HMGB1 has been observed in different types of cell death such as apoptosis, necrosis, and necroptosis [50, 79–84]. Similarly, classical autophagic stimuli such as rapamycin or starvation trigger HMGB1 translocation and release [81]. This process is not associated with lactate dehydrogenase release in the early stage, suggesting that translocation and release of HMGB1 in autophagy is an active process. Reactive oxygen species (ROS) generated in cell

stress induce cell death, survival, or senescence, depending on the concentration of ROS. ROS quencher (e.g. *N*-acetyl cysteine) inhibits starvation- and rapamycin-induced HMGB1 translocation and subsequent autophagy [81]. Knockdown of antioxidant enzyme superoxide dismutase 1 also promotes HMGB1 cytosolic translocation and release in autophagy [85]. These findings suggest that oxidative stress is required for the translocation and release of HMGB1 in autophagy.

BECN1 was originally discovered as a Bcl-2-interacting protein. Bcl-2 binds to BECN1, leading to repression of autophagy [86]. We now know that BECN1 participates in autophagosome formation and plays an important role in the regulation of interplay between autophagy and apoptosis [87]. The levels of HMGB1 affect the interaction between Bcl-2 and BECN1 in autophagy. On one hand, HMGB1 is involved in the regulation of Bcl-2 phosphorylation by activation of the ERK pathway. Ablation of HMGB1 diminishes starvation-induced phosphorylation of both ERK1/2 and Bcl-2 [87]. Phosphorylation of Bcl-2 inhibits interaction between Bcl-2 and BECN1. On the other hand, cytosolic HMGB1 has been identified as a direct BECN1-binding protein in tumor and nontumor cells. HMGB1 competes with Bcl-2 for interaction with BECN1 and orients BECN1 to autophagosomes in response to starvation. Structurally, C23 and C45 are required for HMGB1 to bind to BECN1 [87]. Mutation of C23 and C45 in HMGB1 results in the loss of their ability to mediate autophagy. Moreover, C106S mutation of HMGB1 results in much higher cytoplasmic levels of HMGB1 and demonstrates enhanced binding to BECN1, leading to the subsequent dissociation of Bcl-2 from BECN1. Knockdown of HMGB1 finally inhibits the formation of the BECN1- PIK3C3 complex in autophagy.

In addition to the redox state of HMGB1, several proteins such as ULK1, FIP200, nuclear accumbens-1 (NAC1), p53, SNCA/ α -synuclein, and gamma-interferon inducible lysosomal thiol reductase (GILT) have been demonstrated to positively or negatively regulate HMGB1-BECN1 complex formation in several cells.

Different from other ATGs, ULK1 is a serine/threonine-protein kinase. FIP200 (FAK family kinase-interacting protein of 200 kDa) was identified in a two-hybrid screen with the tyrosine kinase Pyk2. Both ULK1 and FIP200 are involved in the formation of ULK1-ATG13-FIP200 complex in triggering vesicle nucleation during autophagy [88–91]. The formation of the ULK1-ATG13-FIP200 complex is not affected by HMGB1. However, knockdown of ULK1 or FIP200 inhibits HMGB1-BECN1 complex formation. This increases cell death in osteosarcoma cells following anticancer agent treatment [92]. Thus, the HMGB1-BECN1 complex functions as a downstream signal from ULK1-mATG13-FIP200 complex formation in the induction of autophagy.

NAC1 is a nuclear protein that belongs to the POZ/BTB (Pox virus and zinc finger/bric-a-brac tramtrack broad complex) domain family. NAC1 can bind and increase HMGB1 translocation from the nucleus to the cytosol and subsequent HMGB1-BECN1 complex formation in response to cisplatin [93]. Suppression of NAC1 expression limits HMGB1-BECN1 complex formation and impairs the autophagic response and enhanced anticancer activity of cisplatin in tumor cells [93].

p53, the most common tumor suppressor, plays both transcription-dependent and -independent roles in the regulation of apoptosis, autophagy, metabolism, cell cycle progression, and many other processes. Cytosolic p53 is a negative regulator of autophagy through a transcription-independent mechanism [94] whereas nuclear p53 is a positive regulator of autophagy by a transcription-dependent mechanism [95, 96]. A number of studies have demonstrated a nuclear interaction between HMGB1 and p53 in the regulation of gene expression [97–100]. The interaction between HMGB1 and p53 in the nucleus and cytosol is increased in colon cancer cells following starvation-induced autophagy [101]. Importantly, p53-HMGB1 complexes regulate cytosolic translocation of the reciprocal protein and levels of autophagy. Loss of p53 increases HMGB1 cytosolic translocation and HMGB1- BECN1 complex formation, which results in autophagy induction [101]. In contrast, loss of HMGB1 increases p53 cytosolic translocation, which leads to autophagy inhibition [101]. This dynamic location change between p53 and HMGB1 affects the levels of autophagy and anticancer activity of chemotherapy in colon cancer cells [102].

SNCA is expressed predominantly in the brain, where it is concentrated in presynaptic nerve terminals. The deposition of the abundant presynaptic brain protein SNCA as an aggregating fibrillary in neurons or glial cells is a hallmark lesion in a subset of neurodegenerative disorders. Autophagy contributes to SNCA clearance. Interestingly, aggregated SNCA may inhibit autophagy by blocking the cytosolic translocation of HMGB1 and subsequent HMGB1-BECN1 binding in PC12 cells [103]. Thus, HMGB1 may be a new target for drug intervention to restore the deficient autophagy caused by SNCA in neurodegenerative disorders.

GILT is a lysosomal thiol reductase, which can reduce protein disulfide bonds at a low pH. The enzyme is expressed constitutively in antigen-presenting cells (e.g., B cells, DCs, monocytes, and macrophages) and is induced by γ interferon in endothelial cells and tumor cells. GILT may negatively regulate HMGB1-BECN1 complex formation in response to oxidative stress [104]. Loss of GILT increases the cytosolic translocation of HMGB1 and subsequent autophagy, which contributes to diminished superoxide dismutase 2 expression and elevated superoxide production.

4.3. Extracellular HMGB1 in autophagy

HMGB1 release is a critical regulator of apoptosis and autophagy in response to metabolic and therapeutic stress [105]. Treatment with reduced but not oxidized HMGB1 protein increases the accumulation of LC3 puncta associated with induced LC3-II formation, reduced expression of SQSTM1, and suppressed BECN1-Bcl-2 complex formation [16]. However, the HMGB1 C106A mutant protein significantly decreases autophagy compared with wild-type reduced HMGB1 protein [16]. Moreover, knockout of BECN1 inhibits reduced HMGB1-induced autophagy, suggesting that BECN1 is required for reduced HMGB1-induced autophagy. Interestingly, oxidized HMGB1 may trigger mitochondria-mediated apoptosis by activation of CASP-3 and -9 [16].

Multiple surface receptors, including TLR2, TLR4, and AGER have been demonstrated to mediate HMGB1 activity. C106 is required for HMGB1 binding to TLR4 and activation of cytokine release in macrophages. AGER is a transmembrane receptor of the immunoglobulin

gene superfamily encoded within the class III region of the major histocompatibility locus. RAGE activation has been implicated in infection and sterile inflammation, as well as in cancer, diabetes, and Alzheimer's disease. The interaction between AGER and its ligands, including HMGB1, promotes proinflammatory signal pathway activation and the formation of neutrophil extracellular traps partly through upregulation of autophagy [17, 106, 107]. AGER promotes anticancer agent-induced autophagy by regulating MTOR activation and BECN1-PIK3C3 complex formation [108, 109]. Knockdown of AGER, but not TLR4 in cancer cells diminishes HMGB1-induced autophagy [16]. Moreover, AGER contributes to HMGB1-induced autophagy in a BECN1-dependent manner in cancer cells. However, it is unclear which receptor is required for oxidized HMGB1-induced apoptosis. In addition to HMGB1, AGER is required for IL6- and hypoxia-induced autophagy in pancreatic cancer cells, suggesting an important role of RAGE-mediated autophagy in the pancreatic tumor microenvironment [106, 110].

5. Transcriptional regulation of HMGB1 in autophagy

Transcription factors such as p53 [111], c-Myc [112], and Kruppel-like factor-4 [113] have been reported to regulate mRNA expression of HMGB1 in several cells. These transcription factors are also important for autophagy. In addition to transcription factors, microRNAs (miRNAs) play an important role in the regulation of HMGB1 expression. miRNAs are a class of post-transcriptional regulators of gene expression. They are short (about 22 nucleotide) RNA sequences that bind to complementary sequences in the 3' untranslated region (3'UTR) of multiple target messenger RNAs (mRNAs). At the molecular level, miRNAs restrain the production of proteins by affecting the stability of their target mRNA and/or by downregulating their translation. We recently demonstrated that MIR34A is a potent inhibitor of autophagy by suppression of HMGB1 (but not sirtuin 1) expression in the retinoblastoma cell [114]. MIR34A directly targets HMGB1 mRNA and inhibits HMGB1 protein levels, thereby preventing autophagosome activation [114]. Targeting the MIR34A-HMGB1 pathway inhibits autophagy and increases apoptosis in response to chemotherapy.

Another study suggests that MIR22 controls autophagy by regulating HMGB1 protein levels [115]. MIR22 is an evolutionally conserved miRNA that is highly expressed in various tissues and cancer cells. MIR22-mediated transcriptional regulation of HMGB1 inhibits autophagy and chemotherapy resistance in osteosarcoma cells [115]. The human let-7 family of microRNAs contains 13 members that are major players in the regulation of gene expression. HMGB1 is another important direct target of MIR-let-7f-1 in medulloblastoma cells [116]. Overexpression of MIR-let-7f-1 inhibits HMGB1 expression and subsequent autophagy in medulloblastoma cells following treatment with cisplatin [116]. The complex interactions of HMGB1 expression by miRNAs and transcription factors in autophagy must be further investigated and will likely impact tumor treatment in the future.

6. Post-translational modification of HMGB1 in autophagy

Autophagy is mainly regulated by post-translational and lipid modifications of ATG proteins. HMGB1 also undergoes extensive post-translational modifications, including reversible and terminal acetylation [117], poly-ADP-ribosylation [118, 119], phosphorylation [120], and oxidation [121]. These post-translational modifications have been demonstrated to influence HMGB1's DNA chaperone activity, subcellular localization, and extracellular DAMP activity. We have discussed above that the redox status of HMGB1 affects autophagy. Unlike other members of the tumor necrosis factor (TNF) superfamily, the TNF (ligand) superfamily, member 10 (TNFSF10/TRAIL) selectively activates CASP8 and induces apoptosis in cancer cells (but not normal cells) *in vitro* and *in vivo*. HMGB1 is specifically poly-ADP-ribosylated (PAR) by PAR polymerase-1 (PARP1) in pancreatic cancer cells. This HMGB1 modification contributes to TNFSF10 resistance through upregulation of autophagy and suppression of apoptosis [122]. PARP1 is an ADP-ribosylating enzyme critical for initiating various forms of DNA repair in nucleus. Activation of PARP1 mediates TNFSF10-induced poly-ADP-ribosylation and subsequent translocation of HMGB1 from the nucleus to the cytosol. Inhibition of PARP1 expression or activity via shRNA knock-down or pharmacologic inhibitor PJ-34 significantly limits TNFSF10-induced poly-ADP-ribosylation and the subsequent cytoplasmic translocation of HMGB1 in human pancreatic cancer cells [122]. Importantly, activation of PARP1 promotes HMGB1-BECN1 complex formation, which leads to autophagy following TNFSF10 treatment. Transfection of HMGB1 C106S mutant cDNA into PARP1-knockdown cancer cells increases cytosolic HMGB1 level, LC3-II expression, and TNFSF10 resistance. These findings suggest that cytoplasmic HMGB1 is sufficient to trigger autophagy and TNFSF10 resistance in PARP1-deficient cancer cells [122]. Compared with C106S mutation, the C23S and C45S mutations fail to restore TNFSF10-induced HMGB1-BECN1 complex formation, LC3 turnover, and resistance to apoptosis in HMGB1-knockdown pancreatic cancer cells. Thus, PARP1-HMGB1-BECN1-mediated autophagy inhibits TNFSF10-induced apoptosis by suppression of CASP8 activity [122]. It will be interesting to test whether other post-translational modifications of HMGB1 directly activate autophagy under stress.

7. HMGB1-mediated autophagy in disease

The role of autophagy in cancer is complex and is likely dependent on tumor type and stage [123]. On one hand, autophagy plays a tumor suppressor role by preventing genome instability, limiting oxidative injury, reducing the inflammatory response, and inhibiting angiogenesis. On the other hand, autophagy functions as a survival mechanism in tumor development. Upregulation of autophagy promotes the growth of established tumors by sustaining energy metabolism and cell proliferation. In addition, increased autophagy leads to therapy resistance by diminishing regulated cell death. A number of studies indicate that HMGB1-mediated autophagy can enable tumor cell survival by inhibition of apoptosis, which can lead to

therapeutic resistance [92, 93, 102, 122, 124–130]. It remains to be determined whether HMGB1-mediated autophagy contributes to the suppression of tumorigenesis [131, 132].

Autophagy regulates inflammation through interfering with innate immune signaling pathways, including inflammasome activation and proinflammatory cytokine release [133, 134]. We and others have demonstrated that activation of autophagy contributes to HMGB1 release in immune and nonimmune cells [84]. Inflammasomes are protein complexes in the innate immune system that regulate the activation of CASP1 or CASP11 and induce IL-1 β and IL-18 release in response to infection or tissue injury. Conditional depletion of HMGB1 in myeloid cells renders mice more sensitive to *Listeria monocytogenes* infection and endotoxic shock [135] partly through downregulation of autophagy. This in turn promotes inflammasome activation and IL-1 β release in macrophages [135]. Cytosolic HMGB1 in intestinal epithelial cells suppresses inflammation-associated cellular injury by controlling the switch between the proautophagic and proapoptotic functions of BECN1 and ATG5 during inflammation [136]. Moreover, conditional knockout of HMGB1 in the pancreas and liver promotes pancreatitis [137] and liver ischemic reperfusion [138], which are sterile inflammatory diseases without infection. Additionally, HMGB1 and BECN1 are co-expressed in the invading T cells in the muscle tissue of myositis patients, which is required for T-cell survival and function [139]. The underlying molecular mechanism of HMGB1-mediated autophagy in inflammation and immunity remains to be further explored.

Most neurodegenerative diseases that afflict humans are associated with the intracytoplasmic deposition of aggregate-prone proteins in neurons and with autophagy dysfunction. Impairment of HMGB1-mediated autophagy has been implicated in the increased protein misfolding and aggregation in neurodegenerative disease [140, 141]. In addition, HMGB1 has recently been indicated to be involved in the autophagy inhibition caused by SNCA overexpression, implying a direct role in modulating the autophagic degradation of SNCA [103].

8. Conclusion

HMGB1 is a nuclear protein and stress sensor that plays a critical role in various physiological and pathological processes, including autophagy. Autophagy is the major pathway involved in the degradation of proteins and organelles, cellular remodeling, and survival during stress. HMGB1 plays important intranuclear, cytosolic, and extracellular roles in the regulation of autophagy [142]. Cytoplasmic HMGB1 is a novel BECN1-binding protein active in autophagy. Extracellular HMGB1 induces autophagy in an AGER-dependent manner. Nuclear HMGB1 contributes to mitophagy by regulation of HSPB1 expression. HMGB1-dependent autophagy promotes chemotherapy resistance, [92, 93, 101, 108, 114, 127, 128, 143–145], sustains the tumor metabolism requirement [16, 146] and T-cell survival, [139], prevents polyglutamine aggregates [140] and excitotoxicity [141], and protects against endotoxemia, bacterial infection, and ischemia-reperfusion injury [135, 147–149]. The role of HMGB1 in autophagy is clearly complex and tissue dependent [142]. HMGB1 is not required for starvation-induced autophagy

in mice with hepatocyte-specific HMGB1 deletion, suggesting that an HMGB1-independent autophagy pathway exists in different organs [150]. Indeed, mice with hepatocyte-specific HMGB1 deletion have a different phenotype following different stressors [151, 152]. Targeting the HMGB1-mediated autophagy pathway may be required to address whether or not this approach is therapeutically advantageous in human disease.

Acknowledgements

We apologize to the researchers who were not referenced due to space limitations. We thank Christine Heiner (Department of Surgery, University of Pittsburgh) for her critical reading of the manuscript. This work was supported by the USA National Institutes of Health (R01GM115366 and R01CA160417 to D.T.) and the Natural Science Foundation of Guangdong Province (2016A030308011 to D.T.).

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