REVIEW ARTICLES

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High-Mobility Group Box 1 (HMGB1) and Autophagy in Acute Lung Injury (ALI): A Review

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Acute lung injury (ALI) is a life-threatening clinical syndrome in critically ill patients. The identification of novel biological markers for the early diagnosis of ALI and the development of more effective treatments are topics of current research. High mobility group box-1 protein (HMGB1) is a late inflammatory mediator associated with sepsis, malignancy, and immune disease. Levels of HMGB1 may reflect the severity of inflammation and tissue damage, indicating a potential role for HMGB1 as a prognostic biomarker in ALI, and a potential target for blocking inflammatory pathways. Several studies have shown that HMGB1 regulates autophagy. Autophagy, or type II programmed cell death, is an essential biological process that maintains cellular homeostasis. Studies have shown that HMGB1 and autophagy are involved in the pathogenesis of many lung diseases including ALI but the specific mechanisms underlying this association remain to be determined. This review aims to provide an update on the current status of the role of HMBG1 and autophagy in ALI.

MeSH Keywords: **Acute Lung Injury • Autophagy • HMGB1 Protein**

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Background

Acute lung injury (ALI) is a severe condition that occurs in patients in intensive care units and has a mortality rate of 35–40% [1]. Clinical treatment of ALI focuses on alleviating breathing difficulties using drugs that include hormones and bronchodilators and using mechanical ventilation [2,3]. ALI may occur in association with severe infection, shock, trauma, burns, or aspiration. In ALI, there is an increase in pulmonary inflammation and vascular permeability, which lead to further clinical effects, including hypoxemia [4–7].

The pathogenesis of ALI involves a cascade of inflammatory mediators released by neutrophils, macrophages, endothelial cells, and mast cells that result in increased pulmonary microvascular permeability, interstitial and alveolar pulmonary edema, atelectasis, and hyaline membrane formation, resulting in acute hypoxic respiratory insufficiency or respiratory failure [8,9]. Therefore, elucidation of the underlying molecular mechanisms associated with inflammation in ALI may be helpful in identifying new therapeutic targets.

High mobility group box-1 protein (HMGB1) is a conserved non-histone nuclear protein that is widely distributed in the lung, brain, liver, heart, kidney, and other organs. HMGB1 participates in the processes of replication, recombination, transcription, and DNA repair. HMGB1 plays an important role in inflammatory processes [10]. In response to lipopolysaccharide (LPS) treatment, proinflammatory factors, including interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and HMGB1 are expressed and lead to microvessel formation, enhance cell migration, facilitate cell proliferation [11], and promote inflammation [12,13]. HMGBl is a late inflammatory mediator that can be found extracellularly and can induce ALI and apoptosis and autophagy by promoting nuclear factor (NF)-κB nuclear translocation that leads to the release of inflammatory cytokines. Inflammatory cytokines further promote the release of HMGBl, resulting in a positive feedback loop that amplifies the inflammatory cascade [10,14–16]. Extracellular HMGB1 binds to Toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE), which activates intracellular P38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase 1/2 (ERK1/2), NF-κB, and other downstream signaling pathways. This cascade results in the secretion of transforming growth factor (TGF)-β1, platelet-derived growth factor (PDGF), and increased tissue injury [17–20].

Recently, HMGB1 has been shown to play an essential role in the regulation of autophagy. Autophagy involves the degradation of the cell by the cell's lysosomes. Activation of HMGB1-related signals and autophagy are closely related to the development of respiratory diseases that include ALI, asthma, and pulmonary fibrosis [21–24]. This review aims to provide an update on the current status of the role of HMBG1 and autophagy in ALI.

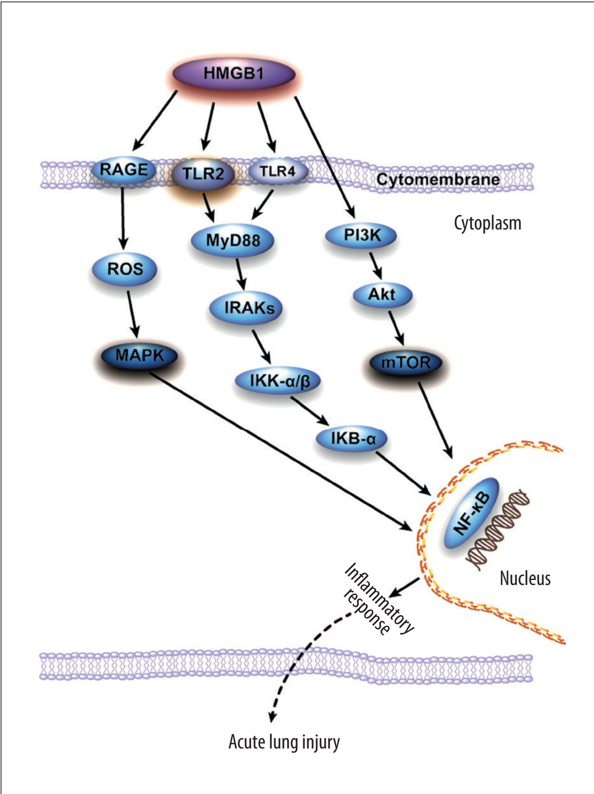

Figure 1. High-mobility group box-1 (HMGB1)-associated signaling transduction pathways in acute lung injury (ALI). Extracellular high-mobility group box-1 (HMGB1) binds to receptors, including receptor for advanced glycation end products (RAGE), Toll-like receptor 2 (TLR2), and TLR4 on the cell membrane, activates reactive oxygen species (ROS), myeloid differentiating factor 88 (MyD88), and PI3K pathways, and leads to the release of tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and other cytokines which contribute to acute lung injury (ALI).

The Role of HMGB1 in Acute Lung Injury (ALI)

The pathogenesis of ALI involves disruption of the balance between oxidation and anti-oxidation, which results in uncontrolled inflammation [25,26]. Recent studies have shown that the levels of HMGB1 were significantly increased in the plasma and lung in a mouse model of lipopolysaccharide (LPS)-induced ALI, supporting the role of HMGB1 as a regulator of ALI [27]. The downstream effects of HMGB1 that may lead to the development of ALI include neutrophil infiltration, pulmonary hemorrhage, injury of lung parenchymal cells, and inflammatory cytokine release, which eventually leads to lung tissue injury [28,29]. Figure 1 shows that following stimulation by LPS,

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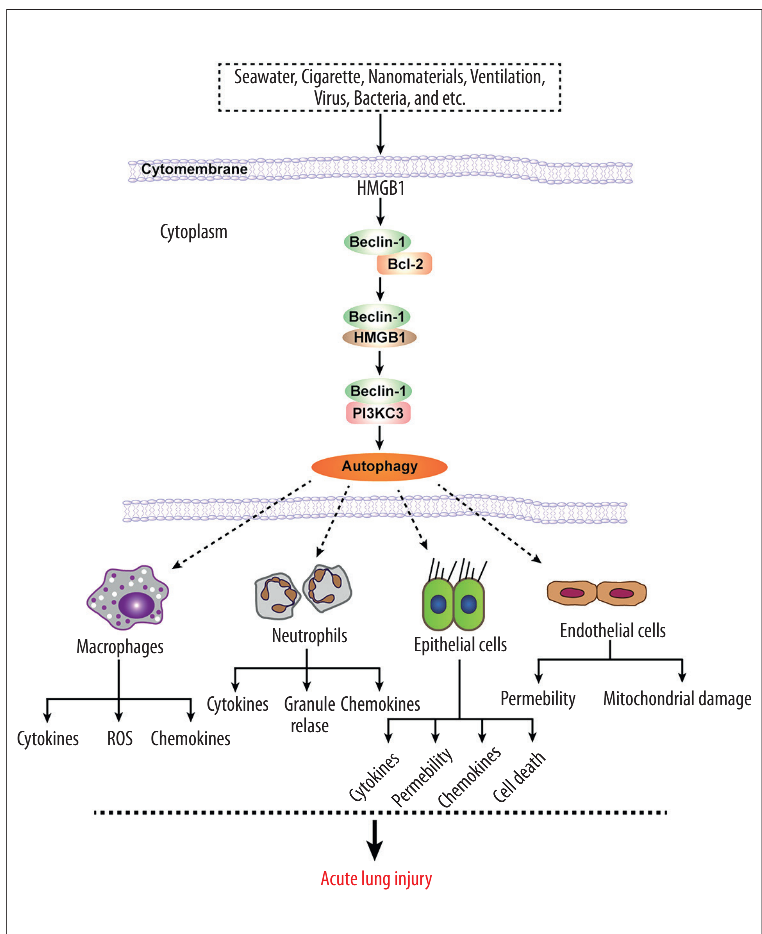

Figure 2. The role of high-mobility group box-1 (HMGB1) and autophagy in acute lung injury (ALI). The black arrows show the relationships between the stimuli that coordinate high-mobility group box-1 (HMGB1) and autophagy in a cell-dependent manner. The final effects of these interactions may vary, depending on the outcome of interactions between cell types.

HMGB1 is released into the extracellular space and binds to specific receptors, including RAGE, TLR2, and TLR4, and induces the production of inflammatory cytokines, chemokines, adhesion molecules, and reactive oxygen species (ROS) that aggravate inflammation and injury. TLR inhibitors have been shown to block this cascade, downstream of HMGB-1 [30].

Following binding to its receptor, RAGE, HMGB1activates NF-κB, and mitogen-activated protein kinases (MAPK) signal pathways, to mediate inflammatory molecules such as TNF-α, IL-1β, and RAGE (Figure 1). RAGE activation can serve as a positive feedback loop to promote further expression of HMGB1. RAGE knockout mice have been shown to resist endotoxin-induced lung injury [28,31], which indicates that the HMGB1-RAGE cascade amplifies the inflammatory response. Also, RAGE inhibitors have been shown to inhibit the cascade effects triggered by HMGB-1 [32]. This finding was confirmed by Achouiti et al. [33] who reported that HMGB1 inhibition and suppression of the RAGE gene reduced Staphylococcus aureus-induced lung injury in mice.

HMGB1 binds to TLR4 receptor and activates the interleukin-1 receptor-associated kinase (IRAK) pathway by activating myeloid differentiating factor 88 (MyD88) [34]. Subsequently, activation of IKK-α/IKK-β leads to the phosphorylation and degradation of IκB-α, which further activates NF-κB and the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. HMGB1 also induces inflammation through the PI3K/AKT/mTOR pathway [34]. The use of the HMGB1 inhibitor, glycyrrhizin, or the use of the HMGB1 short-interfering RNA (siRNA) effectively inhibited the HMGB1-mediated TLR4/NF-κB and PI3K/AKT/mTOR pathways [35–39]. Antibodies to HMGB1 were found to attenuate endotoxin-induced lung injury but did not reduce the early release of TNF-α and IL-1β, indicating that HMGB1 regulated endotoxin-induced ALI in the later stages (Figure 2) [23,34].

The Role of Autophagy in ALI

Autophagy is an intracellular process that delivers soluble macromolecules, organelles, and other cytoplasmic contents to lysosomes for degradation. There are three different types of autophagy, macro-autophagy, micro-autophagy, and chaperone-mediated autophagy [40]. Macro-autophagy delivers cargo to lysosomes by forming double-membrane autophagosomes. Micro-autophagy mediates direct capturing of the

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cargo by the lysosomes without the formation of autophagosomes. Chaperone-mediated autophagy involves selective degradation of the target proteins directly into the lysosome which is delivered by chaperones [41,42]. Macro-autophagy, or autophagy, has received the most attention from recent research, and the main type of autophagy associated with ALI. The process of autophagy consists of sequential steps of nucleation, autophagosome formation, the fusion of autophagosome with lysosomes to form autolysosomes and, finally, the degradation of cargo in autolysosomes by the activity of lysosomal proteolytic enzymes. The degraded products are further utilized by the cells [43–45].

Conversion of cytosolic microtubule-associated protein-1 light chain-3 LC3-I to a lipidated LC3-II has been the gold standard method for measuring autophagy. The conversion of LC3B-I to LC3B-II in epithelial cells is augmented in response to hyperoxia. Tanaka et al. [46] reported that LC3B interacts with the apoptosis-related gene, Fas, which regulates hyperoxia-induced cell death in epithelial cells. Also, the interaction between p62, LC3B, and caspase-8 may play a key role in the regulation of Fas signaling pathway by LC3B.

Autophagy may serve a potential target for treating hyperoxia-induced ALI. A study by Dan et al. [26] showed that autophagy had a protective role in ALI induced by ischemia-reperfusion injury and that the ERK1/2 signaling pathway had a positive regulatory effect in the setting of ALI caused by ischemia-reperfusion injury. Li et al. [47] studied autophagy in a mouse model of ALI induced by the third-generation polyamidoamine dendrimer (PAMAM G3). However, inhibition of autophagy reduced lung injury and pulmonary edema and improved survival rate. PAMAM G3-induced ALI is caused by the inhibition of the Akt-TSC2-mTOR signaling pathway in epithelial cells [47]. Recent studies have shown that HMGB1 affects autophagy.

The Role of HMGB1 and Autophagy in ALI

HMGB1 has been shown to be associated with autophagy in the development of lung diseases that include asthma, chronic obstructive pulmonary disease (COPD), tuberculosis, lung cancer, and ALI. HMGB1 and autophagy have been studied in animal models of ALI induced by bacterial infection, sepsis, seawater aspiration, and other stimuli. Autophagy activators, such as rapamycin, and autophagy inhibitors, including 3-methyladenine (3-MA) were used in most of these studies on HMGB1 and autophagy in ALI. HMGB1 may regulate autophagy at the intracellular, nuclear, or extracellular level. The interaction between HMGB1 and Beclin-1 in the cytoplasm is the primary regulator of ALI-induced autophagy. However, the specific mechanisms of the interaction between HMGB1 and autophagy have been found to vary in different cell types including macrophages, neutrophils, epithelial cells, and endothelial cells, and are dependent on the nature of the triggering injury (Table 1).

Macrophages, HMGB1, and ALI

In the lungs, interstitial tissue macrophages and alveolar macrophages play an important role in the initiation of inflammation in response to infection and injury [5,48]. During inflammation, macrophages accumulate in the lungs to maintain and further exacerbate the inflammatory response. Autophagy in macrophages interacts with intracellular inflammatory pathways to promote the release of HMGB1. Zhang et al. [49] studied mechanical ventilation-induced lung injury and reported that high tidal volume could rapidly activate autophagy in alveolar macrophages, resulting in an increased inflammatory response. Silencing of the autophagy-related 5 (ATG5) gene in lung macrophages, or treatment with 3-MA, significantly reduced activation of the NLRP3 inflammasome and lung injury caused by mechanical ventilation [49]. Autophagy also interacts with the inflammasome through a complex of the cytoplasmic pathogen recognition receptor in the inflammasome, which activates caspase-1 and induces IL-1β and IL-18 secretion. Inflammasome activation in the macrophage by autophagy-related pathways can also promote HMGB1 secretion [50,51].

Autophagy in macrophages inhibits the inflammatory responses in LPS treated cells. Dysfunctional mitochondria were shown to accumulate in autophagy-deficient mouse macrophages which subsequently activated the NALP3 inflammasome, increased mitochondrial ROS-induced inflammation, and increased mortality in mice [52]. Harris et al. [53] found that proinflammatory cytokines bound to autophagosomes following treatment of macrophages with Toll-like receptor ligands. Activation of autophagy with rapamycin has been shown to induce the degradation of proinflammatory cytokines and reduced the secretion of late cytokines. In another study, silica exposure enhanced autophagic activity in cultured bone marrow-derived macrophages and alveolar macrophages *in vivo* [24]. Impaired autophagy in myeloid cells in ATG5fl/flLysM-Cre+ mice resulted in enhanced cytotoxicity and an inflammatory response associated with the expression of IL-18 and release of HMGB1 in lung lavage fluid after exposure to silica, which contributed to acute inflammation or chronic lung disease [24].

Yanai et al. [54] showed that cytosolic HMGB1-mediated autophagy in macrophages protected mice from endotoxemia and bacterial infection induced by LPS or *Listeria monocytogenes*, respectively. HMGB1 in the cytoplasm binds to the autophagic protein Beclin1, promotes dissociation of Beclin-1 from the apoptosis inhibitor Bcl-2, and facilitates binding of Beclin1 and class III inositol 3 kinase (PI3K ClassIII)/Vsp34 that

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Table 1. Summary of the role of high-mobility group box 1 (HMGB1) and autophagy in animal models of acute lung injury (ALI).

Cell type or tissue	ALI model (s)	Major outcome(s) related to HMGB1 and autophagy	References
Macrophage	VILI	Inhibition of autophagy reduced the inflammatory response and lung injury	Zhang et al., 2014 [49]
	LPS	Increased autophagy reduced inflammation and mortality in mice	Nakahira et al., 2011 [52]
	Silica	Impairment of autophagic gene enhanced cytotoxicity and inflammatory response of IL-18 and HMGB1 in lung lavage fluid, aggravating lung injury.	Jessop et al., 2016 [24]
	I/R	Autophagy inhibition reduced DAMPs-triggered production of inflammatory cytokines including HMGB1	Liu et al., 2017 [57]
Neutrophil	LPS	Increased autophagy reduced degranulation and the production of HMGB1	Zhu et al., 2017 [59]
	CS	Increased autophagy reduced cells death and expression of ROS and HMGB1, and attenuated lung injury	Lv et al., 2017 [60]
	HS	Activation of HMGB1/TLR4 signaling pathway in polymorphonuclear neutrophils and upregulation of NOD2 expression in macrophages to influence autophagy and inflammation progress	Wen et al., 2014 [21]
Epithelial cell	Nanoparticle	Autophagy inhibitor rescued cell death and ameliorated ALI in mice	Li et al., 2009 [47]
	LPS	Activated autophagy and limited production of proinflammatory cytokine such as HMGB1	Yen et al., 2013 [70]
	Starvation	Inhibition of HMGB1 translocation from the nucleus to the cytoplasmic thus limiting HMGB1 release and cell death	Tang et al., 2010 [55]
Endothelial cell	LPS	Increased autophagy enhanced cell viability and protected the integrity of the endothelial barrier	Zhang et al., 2018 [76]
	Hypoxia	Autophagy inhibitor promoted translocation of HMGB1 from the cytoplasm to the nucleus, resulting in reducing cell damage	Sachdev et al., 2012 [80]
	CS	Increased HMGB1 elevated the stress response of the endoplasmic reticulum, promoting the occurrence of autophagy and aggravating cell damage	Petrusca et al., 2014 [81]
Lung	CLP	Increased autophagy, reduced inflammatory cytokines such as HMGB1, IL-6 and MCP-1 in serum, alleviated ALI and significantly increased the survival rate of mice	Yen et al., 2013 [70]
		Overexpression of LC3 gene attenuated lung injury/inflammation by increasing autophagic clearance	Lo et al., 2013 [82]
	Seawater	Autophagy was inhibited and the expression of inflammatory cytokines was reduced in bronchoalveolar lavage fluid and alleviated lung injury	Liu et al., 2013, 2014 [93,94]
	H5N1	Inhibition of autophagy alleviated ALI and reduced mortality in mice	Sun et al., 2012 [66], Ma et al., 2011 [100]
	VILI	Knockdown of the autophagy gene improved inflammation and reduced lung injury	López-Alonso et al., 2013 [102]

ALI – acute lung injury; CS – cigarette smoke; CLP – cecal ligation and puncture; DAMPs – damage-associated molecular patterns; HMGB1 – high mobility group box 1; HS – hemorrhagic shock; H5N1 – avian influenza A virus; I-R – ischemia-reperfusion; LPS – lipopolysaccharide; NOD2 – nucleotide-binding oligomerization domain 2; VILI – ventilation-induced lung injury.

activates autophagy [55,56]. Liu et al. [57] showed that alveolar macrophages released damage-associated molecular patterns (DAMP), including HMGB1 and heat shock protein 60 (HSP60) during lung ischemia-reperfusion injury [57]. Alveolar macrophages treated with HMGB1 or HSP60 induced autophagy and inflammation [57]. Knockdown of ATG7 or Beclin-1 significantly reduced the activation of MAPK and NF-κB signaling in DAMPs-treated alveolar macrophages, reducing the

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production of IL-1β, TNF, and IL-12 inflammatory cytokines, which reduced lung injury [57].

Neutrophils, HMGB1, and ALI

In the early stages of ALI, neutrophils degranulate and release proinflammatory cytokines [58,59]. In a mouse model of LPS-induced ALI, ethyl pyruvate treatment reduced autophagy, inhibited neutrophil-derived granule release, and reduced the production of myeloperoxidase (MPO) and proinflammatory cytokines, including HMGB1, in bronchoalveolar lavage fluid (BALF) [59]. Knockdown of the ATG5 gene inhibited autophagy, abrogated the effects of ethyl pyruvate on granules released by neutrophils, and increased the degree of ALI [59]. Lv et al. [60] showed that cigarette smoke activated the platelet-activating factor receptor (PAFR) and enhanced the production of reactive oxygen species (ROS) and the expression of HMGB1. The autophagy inhibitor, 3-MA, suppressed cigarette smoke-induced autophagy in neutrophils, which reduced neutrophil death and lung injury [60]. Tang et al. [61] reported that treatment with HMGB1 induced activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and increased ROS production in neutrophils, induced autophagy, and increased lung damage. Antioxidants, including ethyl pyruvate, reduced the release of HMGB1 and reduced lung injury [61].

The number of neutrophils has been shown to be increased in ALI induced by hemorrhagic shock and that the neutrophils PMNs regulate inflammatory responses by controlling autophagy and activating the HMGB1/TLR4 signaling pathway [21]. Increased expression of nucleotide-binding oligomerization domain 2 (NOD2) in macrophages was shown to be associated with NOD2 ligand muramyl dipeptide and augmentation of lung inflammation [21]. NOD2 signaling also induced autophagy in macrophages, which negatively regulated lung inflammation through feedback suppression of NOD2-RIP2 signaling and inflammasome activation [21].

Epithelial Cells, HMGB1, and ALI

Alveolar epithelial cells are divided into type I and type II pneumocytes. Disruption of epithelial cells leads to loss of normal fluid transport and epithelial barrier permeability [62–64]. Autophagy has been shown to be associated with programmed cell death in alveolar epithelial cells [65]. The autophagy inhibitor, 3-MA, reduced nanoparticle-induced epithelial cell death and ameliorated ALI [47]. Beclin-1 knockdown, or treatment with 3-MA, inhibited autophagic cell death in lung epithelial cells caused by avian influenza A virus (H5N1) infection, reduced ALI and improved the survival rate in mice [66]. Activation of the NF-κB signaling pathway promoted the production of cytokines and chemokines involved in the pathogenesis of ALI [67].

LC3B-siRNA has been shown to block autophagy and reduce apoptosis in bronchial epithelial cells following damage induced by cigarette smoke [68]. TLR4 inhibition or TLR4 knockdown using siRNA inhibited the expression of HMGB1 expression in epithelial cells, inhibited NF-κB and JNK/p38 via TLR4/MyD88-dependent signaling, suppressed proinflammatory cytokine production, and reduced inflammation in lungs exposed to cigarette smoke [69]. In another study, LPS inhibited the expression of the autophagy-related protein LC3 in A549 human alveolar basal epithelial cells [70]. However, treatment with rapamycin promoted autophagy and reduced the production of HMGB1 in response to LPS [70]. Cytosolic HMGB1 regulates apoptosis by protecting the autophagy proteins, Beclin-1 and ATG5, from calpain-mediated cleavage during inflammation. Epithelium-specific HMGB1 deletion was found to increase calpain activation, Beclin-1, and ATG5 cleavage, which caused epithelial cell death, indicating that HMGB1 is essential in mitigating inflammation-related cellular injury by regulating the pro-apoptotic functions of Beclin-1 and ATG5 during inflammation [71]. The release of ROS from epithelial cells during oxidative stress, such as starvation, promoted the binding of HMGB1 to Beclin-1 and increased autophagy. Inhibition of HMGB1 translocation from the nucleus to the cytoplasm has been shown to inhibit autophagy and reduce cell death in ALI [55].

Endothelial Cells, HMGB1, and ALI

Pulmonary vascular endothelial cells are involved in gas exchange in the alveoli and maintain fluid balance in the alveoli and the interstitium. Injury to vascular endothelial cells causes increased capillary permeability, which results in pulmonary edema [72]. Autophagy supports the normal function of vascular endothelial cells. Studies have shown that LPS-induced lung injury causes the release of HMGB1 and enhances pulmonary microvascular endothelial cell permeability [73–75]. Zhang et al. [76] showed that LPS induced pulmonary microvascular endothelial cell permeability, increased the release of lactate dehydrogenase (LDH), decreased cell viability, and inhibited zonula occludens-1 (ZO-1), which is also known as tight junction protein-1 and is a peripheral membrane protein encoded by the TJP1 gene [76]. However, induction of autophagy enhanced endothelial cell viability and protected the endothelial barrier from the harmful effects of LPS [76].

Lee et al. [77] reported that knockdown of autophagic gene LC3B in mice led to massive pulmonary endothelial cell damage and aggravated hypoxia-induced pulmonary hypertension. Autophagy plays an important role in pulmonary vascular remodeling by regulating apoptosis and inducing

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hyperproliferation of pulmonary arterial endothelial cells. Nanoparticles formed by ssATG101-TNP inhibited the expression of autophagy gene ATG101 in pulmonary arterial endothelial cells, inhibited functional autophagy, promoted apoptosis during hypoxia, and increased cell permeability [78]. In contrast, induction of autophagy reversed these effects suggesting that the regulation of autophagy may be a new strategy for the treatment of diseases involving endothelial injury [78]. Hypoxia-induced activation of autophagy in endothelial cells promoted the release of HMGB1 from the nucleus, while treatment with 3-MA caused translocation of HMGB1 from the cytoplasm to the nucleus and reduced endothelial cell damage [78].

Xie et al. [79] found that ischemia-reperfusion injury induced the expression of monocyte chemotactic-induced protein-1 (MCPIP1) and HMGB1, which increased endothelial cell migration and induced autophagy. Treatment with rapamycin aggravated endothelial cell damage [79]. Cytosolic HMGB1 expression was increased in endothelial cells under hypoxic conditions [79]. Furthermore, treatment with HMGB1 has been shown to promote angiogenesis [80]. Neutralization of endogenous HMGB1 markedly inhibited autophagy and impaired angiogenesis [80]. Increased phosphorylation of Akt and increased ceramide secretion in lung vascular endothelial cells in long-term smokers resulted in an increased expression of sphingosine and HMGB1 and increased the endoplasmic reticulum stress response, which promoted autophagy and aggravated endothelial cell injury [81].

Models of Acute Lung Injury

In a mouse model of ALI induced by cecal ligation and puncture, massive leukocyte infiltration, inflammatory cytokine production, and downregulation of the autophagic proteins, LC3II, ATG5, and Rab7 were observed [70]. Administration of activated protein C and rapamycin activated autophagy, reduced inflammatory cytokines, including HMGB1, IL-6, and MCP-1 in mouse serum, reduced the severity of ALI, and improved the survival rate in a mouse model of ALI [70]. Transgenic mice that overexpressed LC3 showed increased autophagosome clearance, decreased cell death and inflammatory cytokines, including TNF-α, IL-6 [82]. In the transgenic mouse model, survival was improved in response to cecal ligation and puncture with treatment with bafilomycin A1, an inhibitor of autophagosome-lysosome fusion [82]. Lee et al. [83] found that carbon monoxide enhanced the expression of the autophagic gene LC3 and Beclin1 in mice after cecal ligation and puncture and promoted phagocytosis of bacteria by macrophages [83]. In contrast, Beclin1 knockout mice were more sensitive to sepsis induced by cecal ligation and puncture and did not respond to carbon monoxide treatment. These mice showed aggravated lung injury and decreased survival rate [83].

In a mouse model of sepsis induced by LPS, the release of HMGB1 caused cell damage, and treatment with an anti-HMGB1 antibody inhibited endotoxin-induced lung inflammation [28,84,85]. The damaging effect of HMGB1 was found to be mediated by the RAGE signaling pathway [86]. Studies have shown that RAGE binds to its ligand and promotes inflammatory responses and signal-regulated kinase phosphorylation, and increases NF-κB activation and p65 expression [87,88]. Binding of HMGB1 to RAGE activates ERK, and ERK further activates death-associated protein kinase (DAPK), phosphorylates Beclin-1, and promotes the dissociation of Beclin1 from Bcl-2 to regulate the level of autophagy [89,90]. Activated MAPK can also phosphorylate Bcl-2 which causes dissociation of Bcl-2 from Beclin1 and regulates autophagy [56]. In the LPS-induced ALI model, excessive autophagy was detected, and treatment with 3-MA inhibited the inflammatory response, decreased the expression of autophagic proteins LC3, ATG5, and Rab7 which was mediated by TLR4-NF-κB pathway, reducing ALI [91]. Also, in a model of ALI that used saturated hydrogen saline downregulation of NF-κB expression resulted in a decrease in Beclin-1 transcription and inhibition of autophagy to reduce ALI [92].

In a seawater-induced model of ALI, 3-MA reduced the production of inflammatory cytokines, including TNF-α and IL-8 in alveolar lavage fluid and reduced lung injury [93]. Liu et al. [94] reported that inhibition of autophagy improved arterial blood gases, lung coefficient, and cytokines that included TNF-α and IL-8 in bronchoalveolar lavage fluid (BALF) and reduced ALI induced by seawater. These results indicate that autophagy plays a detrimental role in seawater-induced ALI which is consistent with its role in other models of ALI [47]. Other factors, such as air pollution [95], and inhalation of chlorinated swimming-pool water [96], which are known to cause acute lung damage, may be associated with the release of HMGB-1 and activation of autophagy, but these are areas that require further study.

Studies in mouse models of pneumonia following infection with H5N1 strain of influenza virus showed that lung damage was mediated by HMGB1 [97–99]. H5N1 infection also induced autophagic cell death in lung epithelial cells [97–99]. Inhibition of autophagy by knockdown of Beclin1, or by treatment with 3-MA, reduced epithelial cell death, alleviated H5N1-induced ALI, and reduced the mortality rate in mice [66,100].

Ding et al. [101] found that mechanical ventilation in mice significantly increased LPS-induced lung injury and HMGB1 expression and increased IL-1β, IL-6, and MIP-2 levels in BALF. HMGB1-mediated lung injury was believed to be associated with the production of proinflammatory cytokines mediated by p38 and NF-κB pathways. López et al. [102] showed that inhibition of NF-κB activation reduced the inflammatory response and reduced lung injury induced by mechanical ventilation in an autophagic ATG4b gene knockout mouse model of ALI.

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Conclusions

There have now been several studies that have provided evidence for the relationship between HMGB1 and autophagy in ALI. HMGB1 interacts with inflammatory cytokines and amplifies the inflammatory response leading to tissue damage. Due to the increased expression of HMGB1 in ALI, HMGBA has a potential role as a biomarker of ALI, which may be used in the diagnosis and prognosis of the disease. Understanding the mechanism of HMGB1 in ALI may also help to identify novel therapeutic targets. Autophagy plays a dual role in ALI (Table 1). Future research should focus on understanding the role of autophagy in ALI which would lay the foundation for developing new treatment strategies. Increased understanding of the changes in the expression of specific genes may help to elucidate the role of HMGB1 and autophagy in different models of ALI (Figure 2). Because autophagy is associated with a range of diseases, including malignancy, neurodegenerative disease, and autoimmune disease, understanding the relationship between HMGB1 and autophagy might also identify novel therapeutic targets for these diseases [42,103,104]. Despite a large number of studies on HMGB1 and autophagy in ALI, there are still questions regarding the mechanisms involved in the relationship between HMGB1 and autophagy in ALI, which requires further research.

Conflict of interest

None.

References:

1. Hayes M, Curley G, Ansari B, Laffey JG: Clinical review: Stem cell therapies for acute lung injury/acute respiratory distress syndrome – hope or hype? Crit Care, 2012; 16(2): 205
2. Tongyoo S, Permpikul C, Mongkolpun W et al: Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: Results of a randomized controlled trial. Crit Care, 2016; 20(1): 329
3. Nieman GF, Andrews P, Satalin J et al: Acute lung injury: how to stabilize a broken lung. Crit Care, 2018; 22: 136
4. Li Y, Li H, Liu S et al: Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. Mol Immunol, 2018; 99: 134–44
5. Fan E, Fan J: Regulation of alveolar macrophage death in acute lung inflammation. Respir Res, 2018; 19(1): 50
6. Fan E, Brodie D, Slutsky A: Acute respiratory distress syndrome: Advances in diagnosis and treatment. JAMA, 2018; 319(7): 698–710
7. Li Y, Wu R, Tian Y et al: RAGE/NF-κB signaling mediates lipopolysaccharide-induced acute lung injury in neonate rat model. Int J Clin Exp Med, 2015; 8(8): 13371–76
8. Herold S, Gabrielli N, Vadász I: Novel concepts of acute lung injury and alveolar-capillary barrier dysfunction. Am J Physiol Lung Cell Mol Physiol, 2013; 305(10): L665–81
9. Nieman G, Gatto L, Habashi N: Impact of mechanical ventilation on the pathophysiology of progressive acute lung injury. J Appl Physiol, 2015; 119(11): 1245–61
10. Luan Z, Hu B, Wu L et al: Unfractionated heparin alleviates human lung endothelial barrier dysfunction induced by High Mobility Group Box 1 through regulation of P38-GSK3β-snail signaling pathway. Cell Physiol Biochem, 2018; 46(5): 1907–18
11. Smolarczyk R, Cichoń T, Jarosz M, Szala S: [HMGB1 – its role in tumor progression and anticancer therapy]. Postepy Hig Med Dosw (Online), 2012; 66: 913–20 [in Polish]
12. Yang Q, Liu X, Yao Z et al: Penehyclidine hydrochloride inhibits the release of high-mobility group box 1 in lipopolysaccharide-activated RAW264.7 cells and cecal ligation and puncture-induced septic mice. J Surg Res, 2014; 186(1): 310–17
13. Musumeci D, Roviello G, Montesarchio D: An overview on HMGB1 inhibitors as potential therapeutic agents in HMGB1-related pathologies. Pharmacol Ther, 2014; 141(3): 347–57
14. Entezari M, Javdan M, Antoine D et al: Inhibition of extracellular HMGB1 attenuates hyperoxia-induced inflammatory acute lung injury. Redox Biol, 2014; 2: 314–22
15. Li N, Liu X, Hong M et al: Sodium butyrate alleviates LPS-induced acute lung injury in mice via inhibiting HMGB1 release. Int Immunopharmacol, 2018; 56: 242–48
16. Lee S, Piao C, Kim G et al: Production and application of HMGB1 derived recombinant RAGE-antagonist peptide for anti-inflammatory therapy in acute lung injury. Eur J Pharm Sci, 2018; 114: 275–84
17. He ZW, Qin YH, Wang ZW et al: HMGB1 acts in synergy with lipopolysaccharide in activating rheumatoid synovial fibroblasts via p38 MAPK and NF-kappaB signaling pathways. Mediators Inflamm, 2013; 2013: 596716
18. Pusterla T, Nèmeth J, Stein I et al: Receptor for advanced glycation endproducts (RAGE) is a key regulator of oval cell activation and inflammation-associated liver carcinogenesis in mice. Hepatology, 2013; 58(1): 363–73
19. Guijarro-Muñoz I, Compte M, Álvarez-Cienfuegos A et al: Lipopolysaccharide activates Toll-like receptor 4 (TLR4)-mediated NF-κB signaling pathway and proinflammatory response in human pericytes. J Biol Chem, 2014; 289(4): 2457–68
20. Mulrennan S, Baltic S, Aggarwal S et al: The role of receptor for advanced glycation end products in airway inflammation in CF and CF related diabetes. Sci Rep, 2015; 5: 8931
21. Wen Z, Fan L, Li Y et al: Neutrophils counteract autophagy-mediated anti-inflammatory mechanisms in alveolar macrophage: Role in posthemorrhagic shock acute lung inflammation. J Immunol, 2014; 193(9): 4623–33
22. Xia F, Deng C, Jiang Y et al: IL4 (interleukin 4) induces autophagy in B cells leading to exacerbated asthma. Autophagy, 2018; 14(3): 450–64
23. Yan J, Li J, Zhang L et al: Nrf2 protects against acute lung injury and inflammation by modulating TLR4 and Akt signaling. Free Radic Biol Med, 2018; 121: 78–85
24. Jessop F, Hamilton RF, Rhoderick JF et al: Autophagy deficiency in macrophages enhances NLRP3 inflammasome activity and chronic lung disease following silica exposure. Toxicol Appl Pharmacol, 2016; 309: 101–10
25. Spragg R, Bernard G, Checkley W et al. Beyond mortality: Future clinical research in acute lung injury. Am J Respir Crit Care Med, 2010; 181(10): 1121–27
26. Zhang D, Li C, Zhou J et al: Autophagy protects against ischemia/reperfusion-induced lung injury through alleviating blood-air barrier damage. J Heart Lung Transplant, 2015; 34(5): 746–55
27. Suda K, Takeuchi H, Ishizaka A, Kitagawa Y: High-mobility-group box chromosomal protein 1 as a new target for modulating stress response. Surg Today, 2010; 40(7): 592–601
28. Abraham E, Arcaroli J, Carmody A et al: HMG-1 as a mediator of acute lung inflammation. J Immunol, 2000; 165(6): 2950–54
29. Kim J, Park J, Strassheim D et al: HMGB1 contributes to the development of acute lung injury after hemorrhage. Am J Physiol Lung Cell Mol Physiol, 2005; 288(5): L958–65
30. Wolfson R, Chiang E, Garcia J: HMGB1 induces human lung endothelial cell cytoskeletal rearrangement and barrier disruption. Microvasc Res, 2011; 81(2): 189–97
31. Sims G, Rowe D, Rietdijk S et al: HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol, 2010; 28: 367–88
32. Rouhiainen A, Kuja-Panula J, Tumova S, Rauvala H: RAGE-mediated cell signaling. Methods Mol Biol, 2013; 963: 239–63

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Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

33. Achouiti A, van der Meer A, Florquin S et al: High-mobility group box 1 and the receptor for advanced glycation end products contribute to lung injury during *Staphylococcus aureus* pneumonia. Crit Care, 2013; 17(6): R296
34. Kwon WY, Suh GJ, Kim KS et al: Glutamine attenuates acute lung injury by inhibition of high mobility group box protein-1 expression during sepsis. Br J Nutr, 2010; 103(6): 890–98
35. Di Candia L, Gomez E, Venereau E et al: HMGB1 is upregulated in the airways in asthma and potentiates airway smooth muscle contraction via TLR4. J Allergy Clin Immunol, 2017; 140(2): 584–87.e588
36. Ojo O, Ryu M, Jha A et al: High-mobility group box 1 promotes extracellular matrix synthesis and wound repair in human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol, 2015; 309(11): L1354–66
37. Jing W, Chunhua M, Shumin W: Effects of acteoside on lipopolysaccharide-induced inflammation in acute lung injury via regulation of NF-κB pathway *in vivo* and *in vitro*. Toxicol Appl Pharmacol, 2015; 285(2): 128–35
38. Zhou R, Luo F, Lei H et al. Liujunzi Tang, a famous traditional Chinese medicine, ameliorates cigarette smoke-induced mouse model of COPD. J Ethnopharmacol, 2016; 193: 643–51
39. Meng L, Li L, Lu S et al: The protective effect of dexmedetomidine on LPS-induced acute lung injury through the HMGB1-mediated TLR4/NF-κB and PI3K/Akt/mTOR pathways. Mol Immunol, 2018; 94: 7–17
40. Fougeray S, Pallet N: Mechanisms and biological functions of autophagy in diseased and aging kidneys. Nat Rev Nephrol, 2015; 11(1): 34–45
41. Parzych K, Klionsky D: An overview of autophagy: Morphology, mechanism, and regulation. Antioxid Redox Signal, 2014; 20(3): 460–73
42. Mizushima N, Levine B, Cuervo A, Klionsky D: Autophagy fights disease through cellular self-digestion. Nature, 2008; 451(7182): 1069–75
43. Subramani S, Malhotra V: Non-autophagic roles of autophagy-related proteins. EMBO Rep, 2013; 14(2): 143–51
44. Levine B, Kroemer G: Autophagy in the pathogenesis of disease. Cell, 2008; 132(1): 27–42
45. Yang Z, Klionsky D: Eaten alive: A history of macroautophagy. Nat Cell Biol, 2010; 12(9): 814–22
46. Tanaka A, Jin Y, Lee S, Zhang M et al: Hyperoxia-induced LC3B interacts with the Fas apoptotic pathway in epithelial cell death. Am J Respir Cell Mol Biol, 2012; 46(4): 507–14
47. Li C, Liu H, Sun Y et al: PAMAM nanoparticles promote acute lung injury by inducing autophagic cell death through the Akt-TSC2-mTOR signaling pathway. J Mol Cell Biol, 2009; 1(1): 37–45
48. Fan T, Huang Z, Wang W et al: Proteasome inhibition promotes autophagy and protects from endoplasmic reticulum stress in rat alveolar macrophages exposed to hypoxia-reoxygenation injury. J Cell Physiol, 2018; 233(10): 6748–58
49. Zhang Y, Liu G, Dull R et al: Autophagy in pulmonary macrophages mediates lung inflammatory injury via NLRP3 inflammasome activation during mechanical ventilation. Am J Physiol Lung Cell Mol Physiol, 2014; 307(2): L173–85
50. Lu B, Nakamura T, Inouye K et al: Novel role of PKR in inflammasome activation and HMGB1 release. Nature, 2012; 488(7413): 670–74
51. Dupont N, Jiang S, Pilli M et al: Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1β. EMBO J, 2011; 30(23): 4701–11
52. Nakahira K, Haspel J, Rathinam V et al: Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol, 2011; 12(3): 222–30
53. Harris J, Hartman M, Roche C et al: Autophagy controls IL-1beta secretion by targeting pro-IL-1beta for degradation. J Biol Chem, 2011; 286(11): 9587–97
54. Yanai H, Matsuda A, An J et al: Conditional ablation of HMGB1 in mice reveals its protective function against endotoxemia and bacterial infection. Proc Natl Acad Sci USA, 2013; 110(51): 20699–704
55. Tang D, Kang R, Livesey K et al: Endogenous HMGB1 regulates autophagy. J Cell Biol, 2010; 190(5): 881–92
56. Kang R, Livesey K, Zeh H et al: HMGB1: A novel Beclin 1-binding protein active in autophagy. Autophagy, 2010; 6(8): 1209–11
57. Liu X, Cao H, Li J et al: Autophagy induced by DAMPs facilitates the inflammation response in lungs undergoing ischemia-reperfusion injury through promoting TRAF6 ubiquitination. Cell Death Differ, 2017; 24(4): 683–93
58. Blázquez-Prieto J, López-Alonso I, Huidobro C, Albaiceta G: The emerging role of neutrophils in repair after acute lung injury. Am J Respir Cell Mol Biol, 2018; 59(3): 289–94
59. Zhu Q, Wang H, Wang H et al: Protective effects of ethyl pyruvate on lipopolysaccharide-induced acute lung injury through inhibition of autophagy in neutrophils. Mol Med Rep, 2017; 15(3): 1272–78
60. Lv X, Liu S, Li K et al: Cigarette smoke promotes COPD by activating platelet-activating factor receptor and inducing neutrophil autophagic death in mice. Oncotarget, 2017; 8(43): 74720–35
61. Tang D, Kang R, Zeh H, Lotze M: High-mobility group box 1, oxidative stress, and disease. Antioxid Redox Signal, 2011; 14(7): 1315–35
62. Matthay M, Ware L, Zimmerman G: The acute respiratory distress syndrome. J Clin Invest, 2012; 122(8): 2731–40
63. Zemans R, Matthay M: What drives neutrophils to the alveoli in ARDS? Thorax, 2017; 72(1): 1–3
64. Johnson E, Matthay M: Acute lung injury: Epidemiology, pathogenesis, and treatment. J Aerosol Med Pulm Drug Deliv, 2010; 23(4): 243–52
65. Green D, Levine B: To be or not to be? How selective autophagy and cell death govern cell fate. Cell, 2014; 157(1): 65–75
66. Sun Y, Li C, Shu Y et al: Inhibition of autophagy ameliorates acute lung injury caused by avian influenza A H5N1 infection. Sci Signal, 2012; 5(212): ra16
67. Pan H, Zhang Y, Luo Z et al: Autophagy mediates avian influenza H5N1 pseudotyped particle-induced lung inflammation through NF-κB and p38 MAPK signaling pathways. Am J Physiol Lung Cell Mol Physiol, 2014; 306(2): L183–95
68. Chen Z, Lam H, Jin Y et al: Autophagy protein microtubule-associated protein 1 light chain-3B (LC3B) activates extrinsic apoptosis during cigarette smoke-induced emphysema. Proc Natl Acad Sci USA, 2010; 107(44): 18880–85
69. Cheng Y, Wang D, Wang B et al: HMGB1 translocation and release mediate cigarette smoke-induced pulmonary inflammation in mice through a TLR4/MyD88-dependent signaling pathway. Mol Biol Cell, 2017; 28(1): 201–9
70. Yen Y, Yang H, Lo H et al: Enhancing autophagy with activated protein C and rapamycin protects against sepsis-induced acute lung injury. Surgery, 2013; 153(5): 689–98
71. Zhu X, Messer J, Wang Y et al: Cytosolic HMGB1 controls the cellular autophagy/apoptosis checkpoint during inflammation. J Clin Invest, 2015; 125(3): 1098–110
72. Stevens T: Functional and molecular heterogeneity of pulmonary endothelial cells. Proc Am Thorac Soc, 2011; 8(6): 453–57
73. Hong G, Zheng D, Zhang L et al: Administration of nicotinamide riboside prevents oxidative stress and organ injury in sepsis. Free Radic Biol Med, 2018; 123: 125–37
74. Shao M, Tang S, Liu B, Zhu H: Rac1 mediates HMGB1-induced hyperpermeability in pulmonary microvascular endothelial cells via MAPK signal transduction. Mol Med Rep, 2016; 13(1): 529–35
75. Chen H, Xie K, Han H et al: Molecular hydrogen protects mice against polymicrobial sepsis by ameliorating endothelial dysfunction via an Nrf2/HO-1 signaling pathway. Int Immunopharmacol, 2015; 28(1): 643–54
76. Zhang D, Zhou J, Ye L et al: Autophagy maintains the integrity of endothelial barrier in LPS-induced lung injury. J Cell Physiol, 2018;2 33(1): 688–98
77. Lee S, Smith A, Guo L et al: Autophagic protein LC3B confers resistance against hypoxia-induced pulmonary hypertension. Am J Respir Crit Care Med, 2011;1 83(5): 649–58
78. Du J, Xu Z, Liu Q et al: ATG101 single-stranded antisense RNA-loaded triangular DNA nanoparticles control human pulmonary endothelial growth via regulation of cell macroautophagy. ACS Appl Mater Interfaces, 2017; 9(49): 42544–55
79. Xie X, Zhu T, Chen L et al: MCPIP1-induced autophagy mediates ischemia/reperfusion injury in endothelial cells via HMGB1 and CaSR. Sci Rep, 2018; 8(1): 1735
80. Sachdev U, Cui X, Hong G et al: High mobility group box 1 promotes endothelial cell angiogenic behavior *in vitro* and improves muscle perfusion *in vivo* in response to ischemic injury. J Vasc Surg, 2012; 55(1): 180–91
81. Petrusca D, Van Demark M, Gu Y et al: Smoking exposure induces human lung endothelial cell adaptation to apoptotic stress. Am J Respir Cell Mol Biol, 2014; 50(3): 513–25
82. Lo S, Yuan S, Hsu C et al: Lc3 over-expression improves survival and attenuates lung injury through increasing autophagosomal clearance in septic mice. Ann Surg, 2013; 257(2): 352–63
83. Lee S, Lee SJ, Coronata AA et al: Carbon monoxide confers protection in sepsis by enhancing beclin 1-dependent autophagy and phagocytosis. Antioxid Redox Signal, 2014; 20(3): 432–42

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84. Wang H, Yang H, Tracey K: Extracellular role of HMGB1 in inflammation and sepsis. J Intern Med, 2004; 255(3): 320–31
85. Wang H, Bloom O, Zhang M et al: HMG-1 as a late mediator of endotoxin lethality in mice. Science, 1999; 285(5425): 248–51
86. Abeyama K, Stern D, Ito Y et al: The N-terminal domain of thrombomodulin sequesters high-mobility group-B1 protein, a novel antiinflammatory mechanism. J Clin Invest, 2005; 115(5): 1267–74
87. Bierhaus A, Schiekofer S, Schwaninger M et al: Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. Diabetes, 2001; 50(12): 2792–808
88. Liliensiek B, Weigand M, Bierhaus A et al: Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response. J Clin Invest, 2004; 113(11): 1641–50
89. Liu L, Yang M, Kang R et al: DAMP-mediated autophagy contributes to drug resistance. Autophagy, 2011; 7(1): 112–14
90. Zhao M, Yang M, Yang L et al: HMGB1 regulates autophagy through increasing transcriptional activities of JNK and ERK in human myeloid leukemia cells. BMB Rep, 2011; 44(9): 601–6
91. Ding D, Xu S, Zhang H et al: 3-Methyladenine and dexmedetomidine reverse lipopolysaccharide-induced acute lung injury through the inhibition of inflammation and autophagy. Exp Ther Med, 2018; 15(4): 3516–22
92. Liu Y, Zhang J: Saturated hydrogen saline ameliorates lipopolysaccharide-induced acute lung injury by reducing excessive autophagy. Exp Ther Med, 2017; 13(6): 2609–15
93. Liu Q, Zhou D, Lin P et al: Participation of autophagy in acute lung injury induced by seawater. Exp Lung Res, 2013; 39(10): 441–52
94. Liu Q, Zhou D, Sun L et al: Bone marrow mesenchymal stem cells ameliorates seawater-exposure-induced acute lung injury by inhibiting autophagy in lung tissue. Pathol Res Int, 2014; 2014: 104962
95. Zhao C, Niu M, Song S et al: Serum metabolomics analysis of mice that received repeated airway exposure to a water-soluble PM2.5 extract. Ecotoxicol Environ Saf, 2018; 168: 102–9
96. Bougault V, TurmelJ, Levesque B, Boulet LP: The respiratory health of swimmers. Sports Med, 2009; 39(4): 295–312
97. An S, Xu L, Li F et al: Triple combinations of neuraminidase inhibitors, statins and fibrates benefit the survival of patients with lethal avian influenza pandemic. Med Hypotheses, 2011; 77(6): 1054–57
98. Alleva L, Cai C, Clark I: Using complementary and alternative medicines to target the host response during severe influenza. Evid Based Complement Alternat Med, 2010; 7(4): 501–10
99. Hou X, Qin J, Zheng X et al: Potential role of high-mobility group box 1 protein in the pathogenesis of influenza H5N1 virus infection. Acta Virol, 2014; 58(1): 69–75
100. Ma J, Sun Q, Mi R, Zhang H: Avian influenza A virus H5N1 causes autophagy-mediated cell death through suppression of mTOR signaling. J Genet Genomics, 2011; 38(11): 533–37
101. Ding N, Wang F, Xiao H et al: Mechanical ventilation enhances HMGB1 expression in an LPS-induced lung injury model. PLoS One, 2013; 8(9): e74633
102. López-Alonso I, Aguirre A, González-López A et al: Impairment of autophagy decreases ventilator-induced lung injury by blockade of the NF-κB pathway. Am J Physiol Lung Cell Mol Physiol, 2013; 304(12): L844–52
103. Glick D, Barth S, Macleod K. Autophagy: Cellular and molecular mechanisms. J Pathol, 2010; 221(1): 3–12
104. Levine B, Kroemer G: SnapShot: Macroautophagy. Cell, 2008; 132(1): 162.e161–e163

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