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REVIEW ARTICLE
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Linking Interaction between Antimicrobial Peptide and High Motility Group Box-1 (HMBG-1) in Bacterial Infection

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Abstract:
Antimicrobial peptides (AMPs) are small proteins that protect against bacterial and fungal infections. Various organisms, including plants, animals, and bacteria, produce them. The HMGB-1 (HMGB-1) protein is produced by both immune cells and bacteria, and its main role is to facilitate the recognition of foreign agents, such as bacteria, by the immune system. AMP can protect against infections by interacting with HMGB-1. This enhances their protective capabilities and reduces inflammation associated with bacterial infections.

Keywords: HMGB-1, Antimicrobial peptide, AMP, Cathelicidin, Defensin, Bacterial infection.

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1. INTRODUCTION

Bacterial infections have a significant impact on the health of the general population. Infections can cause severe illness and even death, so it's crucial to identify and treat harmful bacteria promptly and efficiently [1]. Cells or tissue secrete a molecule called an antimicrobial peptide (AMP) that plays a crucial role in the immune system. Previous research has identified AMPs for their antimicrobial properties, with some even demonstrating antiparasitic or antiviral effects [2]. There are three known classes of AMP in humans: defensin, histatin and cathelicidin. Only one type of cathelicidin exists, and multiple defensins have been identified [3, 4].

It is essential to mention that previous studies have proven the significance of antimicrobial peptides in fighting bacterial infections. Previous research has shown that increasing the level of cathelicidin in the body can successfully treat the symptoms of cystic fibrosis, notably the inability to eliminate microbes in the airway surface fluid. Further research has revealed that this approach may also be utilized to treat lung infections caused by *Pseudomonas aeruginosa* in mice [5]. Current studies and trials have reported using exogenous AMP for ocular treatment [6]. Furthermore, a study was done on mice genetically modified to produce porcine cathelicidin. The study showed that these mice were more resistant to skin infections caused by group A *Streptococcus* [7].

High Mobility Group Box-1 (HMGB-1) is a nuclear DNA-binding protein. HMGB-1 is one of the Damage Associated Molecular Patterns (DAMPs) that activates the innate immune system and is part of the High Mobility Group family [8]. This molecule plays a crucial role in inflammation, immunity, cell growth, proliferation, and cell death. HMGB-1 molecule activates cytokines and chemokines *via* RAGE (Receptor for Advanced Glycation End product) and toll-like receptors, including Toll-like Receptor 2 (TLR2), Toll-like Receptor 4 (TLR4), and Toll-like Receptor 9 (TLR9). It subsequently triggers late signaling pathways such as nuclear factor kappa β (NFκβ), interferon regulatory factor-3 (IRF3), and phosphatidylinositol 3-kinase, which induce the production of proinflammatory cytokines by macrophages, including Tumor necrosis factor α (TNF α), interleukin 1 (IL-1), and interleukin 6 (IL-6) [9].

AMPs not only protect against bacterial infections, but they also could reduce inflammation by interacting with other molecules, such as HMGB-1. Previous research showed that upon stimulation with lipopolysaccharides (LPS), HMGB-1 is released from cells. However, this process can be suppressed by CAP11 (cationic antimicrobial polypeptide with 11-kDa), a member of cathelicidin. CAP11 has been found to inhibit the binding of LPS to target cells, which prevents the release of HMGB-1 and necrotic cell death [10, 11]. The study reviewed the biological features, immunological roles, and experimental reports of HMGB-1 and AMPs on bacterial infection using electronic databases, including PubMed, Google Scholar, and Scopus, from years 2000 to 2023.

2. ANTIMICROBIAL PEPTIDE (AMPs)

Antimicrobial Peptide (AMP), also known as *Host Defense Protein*, can directly kill bacteria, viruses, fungi, and parasites, making it a vital part of the body's defense mechanism against microbes [2, 12].

2.1. Types of AMPs and their Functions

AMPs are key components of the innate immune system. They are categorized into three groups: Defensins (alpha, beta, and theta types), Histatins (mostly found in saliva), and Cathelicidin [3, 4, 13]. The types of AMPs dan their roles in the immune system are shown in Table **1**.

Defensins are antimicrobial peptides expressed by human epithelial and blood cells. They have broad antimicrobial activity and are categorized into two families: α and β-defensins based on cysteine location and disulfide-bridge pattern. α-defensins are prominently expressed by Paneth cells in the small intestine and neutrophils, while β-defensins are more abundantly expressed by various blood and epithelial cells [14]. Histatins are small peptides in human saliva that are rich in histidine. They adopt a random coil conformation in aqueous solvents and an α-helix conformation in non-aqueous solvents [15]. Cathelicidin is a molecule that takes a random coil shape in a hydrophilic environment and forms an alpha-helix structure in a hydrophobic environment. It is derived from the C-terminal end of the human CAP18 protein through a proteolytic process [16].

2.2. Mechanisms of Action of AMPs Against Bacterial Pathogens

Cathelicidin or LL-37 promotes neutrophil recruitment and the chemotaxis of other cells, notably monocytes/ macrophages, to the site of infection by releasing numerous cytokines/ chemokines. Keratinocytes secrete cathelicidin, which promotes wound healing. Cathelicidin also contributes to direct and indirect killing by activating autophagy and boosting monocyte /macrophage maturation. Meanwhile, defensins have both direct and indirect lethal effects, interacting with various target cells and tissues to affect inflammation, immune cell recruitment, and the activation and maturation of various immune cells [33]. Antimicrobial peptides function by changing the permeability of the bacterial cell membrane. This process is a crucial step in the antimicrobial action and cytotoxicity caused by antimicrobial proteins. This mechanism inhibits bacteria' RNA, DNA, and protein production, decreasing bacterial viability [34].

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3. HIGH MOTILITY GROUP BOX-1

3.1. Overview of HMGB-1 and its Roles in the Immune Response

HMG, High Mobility Group proteins bind to chromosomes and play a critical role in transcription, replication, recombination, and DNA repair. They are divided into three families based on their functional domains: HMGA, which has an adenine-thymine domain; HMGB, which has an HMG-box domain; and HMGN, which has a nucleosomal binding domain [35]. HMGB protein plays a crucial role in all DNA-related processes in humans. There are three families of HMGB, namely HMGB-1, HMGB-2, and HMGB-3. HMGB-1 is typically found in the nucleus and is excreted into maturity. In contrast, HMGB-2 and HMGB-3 are only excreted during embryogenesis. HMGB-2 mainly focuses on the lymphoid organs and testes during embryogenesis, while HMGB-3 is evenly distributed throughout the body [8, 36].

HMGB-1 is a protein that binds to nuclear DNA and is known as a part of the Damage Associated Molecular Pattern (DAMP). It has been identified as a critical signal that contributes to necrotic-related inflammation. This protein regulates inflammation, particularly in response to microbial infections [37]. HMGB-1 has three nuclear forms: cytosol/cytoplasm and extracellular. The nuclear form of HMGB-1 plays a crucial role in various DNA

Table 1. Antimicrobial peptides' roles in the immune system.

Antimicrobial Peptides	Roles in the Immune System/Refs.
α Defensin	• Degranulate mast cells [17] • Antimicrobial [18] • Block LPS binding [19] • Chemotactic activity [20] • Immunoadjuvant [21]
B Defensin	• Antimicrobial [18] • Degranulate mast cells [22] • Chemotactic activity [23] • Immunoadjuvant [24]
Theta Defensin	• Antimicrobial [25] • Suppression proinflammatory signals [26]
Histatin	• Antimicrobial [27] • Antifungal [28]
Cathelicidin	• Antimicrobial [29] • Chemotactic activity [30] • Degranulate mast cells [30] • Activation of reepithelization [31] • Regulation of dendritic cell differentiation [32]

Table 2. HMGB-1's roles in the immune system.

HMGB-1's Roles in the Immune System	Refs.
• Inducing VEFG, MMPs and PDGF	[40]
• Promoting cell proliferation	[41]
• Inducing lymphangiogenesis angiogenesis	[42]
• Inducing secretion of cytokines	[43, 44]
• Regulating autophagy and apoptosis	[45, 46]
• Antibacterial	[47]

activities, including replication, repair, recombination, transcription, and genomic stability [8]. HMGB-1 is a DNA-binding protein found in most cell types. It has a positively charged HMG box and a negatively charged chain of aspartic and glutamic acid residues. HMGB1 stabilizes nucleosome structure and regulates gene expression in the nucleus [38].

HMGB-1 gene on chromosome 13q12 has six polymorphic loci. HMGB-1 protein has a molecular weight of 25-30 kDa. It comprises 250 amino acids in three structural domains containing 2 DNA-binding domains (box A and box B) and an acid C-terminal end. Box A induces anti-inflammatory effects, while box B facilitates a proinflammatory response and has two binding sites for TLR4 and RAGE [39]. HMGB-1 protein has two domains, A and B. The domain A helps HMGB-1 bind to damaged DNA and acts as an antagonist, providing anti-inflammatory effects. The heparin-binding domain and thrombin mediated cleavage site also have similar effects. The box domain B is associated with cytokine activity and is stimulated by the release of TNF α and other proinflammatory cytokines in macrophages. It also helps the DNA binding. The TLR4 and RAGE binding sites are crucial for activating cytokine release in macrophages. Meanwhile, the acidic tail acts for antibacterial activity [39] (Table **2**).

3.2. HMGB-1 as a Damage-associated Molecular Pattern (DAMP)

HMGB-1 is signaling cellular damage or stress to the immune system. Its release triggers immune responses, such as inflammation and recruitment of immune cells, vital for combating threats and initiating tissue repair processes [48]. DAMPs, also known as alarmins or endogenous molecules, are signals of alarm and danger released by cells in response to danger or stress and have a main role in the nucleus [49]. HMGB-1 is involved in tissue regeneration and inflammation, dependent on necrotic cells that release it as a chemotactic stimulus for cells expressing receptors activated in the inflammatory response [50]. It also induces the secretion of proinflammatory cytokines by immune cells [51].

3.3. HMGB-1 Release in Response to Bacterial Infection

HMGB-1 is secreted *via* active or passive mechanisms. Active secretion occurs when immunocompetent cells undergo post-translational modifications such as acetylation, phosphorylation, methylation, and redox changes. Passive secretion is mediated by necrotic and apoptotic cell death. HMGB-1 secretion leads to inflammation [39]. HMGB-1 activates NF-κβ by interacting with RAGE, TLR2, TLR4, and TLR9 [52]. Its interaction with LPS, LTA, and CpG enhances TLR-mediated signaling, producing proinflammatory cytokines. It also induces chemotaxis and inflammatory cell recruitment by interacting with CXCL12, which binds to CXCR4 [39]. Additionally, HMGB1-RAGE interaction contributes to the activation of ERK1/2 and JNK caused by viral infection [53].

The interaction of HMGB-1 with LPS from bacteria activates various proinflammatory genes. HMGB-1 is produced by living and dead cells in various tissues, and its secretion induces various proinflammatory cytokines, promoting the chronic inflammatory process. HMGB-1 secretion is also a late-phase mediator of inflammation induced by early proinflammatory cytokines and triggers immunosuppressive and pathological effects that follow the subsequent release of cytokines during infection [44, 54].

Several researchers have examined HMGB-1 levels in infection. HMGB1 was previously identified as a late mediator of sepsis in animal models of systemic endotoxemia [55]. Previous clinical studies have found higher levels of HMGB-1 in infected patients, especially those with pneumonia and peritonitis, compared to healthy individuals. HMGB-1 levels were also higher at the site of infection and even higher in patients with severe sepsis [56, 57]. Meanwhile, another study found no correlation between HMGB-1 and the progression or inflammation status of non-tuberculous mycobacterial (NTM) lung disease and reported lower levels of HMGB-1 in pulmonary TB patients [54].

4. EXPERIMENTAL STUDIES AND FINDINGS: AMP-HMGB-1 INTERACTION IN THE CONTEXT OF BACTERIAL INFECTION

A previous *in vitro* study showed that Lipopolysaccharide (LPS) induces caspase 3 activation and the release of lactate dehydrogenase (LDH) and HMGB-1 from murine macrophage cells. This study also indicated that CAP11 (a cationic antibacterial polypeptide) can inhibit LPS binding to target cells, suppressing the release of HMGB-1 and necrotic cell death [10]. Furthermore, CAP11 may protect against endotoxin shock by suppressing septic mediators produced and released by CD14-positive cells by inhibiting LPS binding to targets [11].

Previous in vivo reports provided interactions between AMP and HMGB-1 in infection from a study using a mouse model treated with LL-37 and HMGB-1. The study findings indicated a relationship between LL-37 and HMGB1. Both were associated with increased chemokine levels in lung tissue homogenates in both mice, resulting in reduced lung tissue regeneration. In a sepsis model, mice administration of LL-37 inhibited the increase of HMGB-1 levels both in peritoneal fluids and plasma. Another study reported an interaction between LL-37 and HMGB-1 using cystitis model mice. This study suggested that LL-37 induces cystitis, and HMGB1, a common RAGE ligand, is involved in this inflammatory process [58-60].

Meanwhile, in clinical studies, LL-37 and HMGB-1 are known ligands of the RAGE receptor. It was demonstrated in a study with patients with COPD that reported elevated both LL-37 and HMGB-1 levels in serum during exacerbation. Another previous study found higher levels of HMGB-1 and Human-beta defensin 3 (HBD3) in acute sepsis patients. Recently, a study showed that severe COVID-19 patients have higher levels of circulating NE-DNA, HMGB1-DNA, and LL-37-DNA complexes. HMGB-1 aids in the secretion of inflammatory cytokines, and LL-37 contributes to cytokine storm induction in COVID-19. These findings suggested that HMGB-1 and LL-37 circulating complexes could exacerbate inflammatory responses in severe cases of COVID-19 [55, 61, 62].

5. FUTURE DIRECTIONS AND CHALLENGES

Antimicrobial peptide and HMGB-1 pathways play significant roles in inflammation. AMPs are involved in regulating levels of chemokines. They can suppress the release of HMGB-1 from cells stimulated by Lipopolysaccharide (LPS), highlighting its potential use in managing conditions where HMGB-1 is overexpressed, such as in cases of inflammation or infection. In the context of antimicrobial strategies, exploring the AMPs and HMGB-1 pathways could be useful as potential targets for drug development.

CONCLUSION

The interaction between AMPs and HMGB-1 is an important factor to fight against bacterial infection. By binding to HMGB-1, AMPs can enhance their protective capabilities and reduce inflammation associated with a bacterial infection. This interaction is essential to fight against bacterial infections and will continue to be studied in the future.

LIST OF ABBREVIATIONS

AMP	=	Anti-Microbial Peptide
HMGB-1	=	High Mobility Group Box-1
DAMP	=	Damage Associated Molecular Patterns
RAGE	=	Receptor for advanced glycation end product
TLR2	=	Toll-like Receptor 2
TLR4	=	Toll-like Receptor 4
TLR9	=	Toll-like Receptor 9
IRF3	=	Interferon regulatory factor 3
TNF-α	=	Tumor necrosis factor α
IL-1	=	Interleukin 1
IL-6	=	Interleukin 6
NFκβ	=	Nuclear factor kappa β
LPS	=	Lipopolysaccharides
CAP11	=	Cationic antimicrobial polypeptide with 11-kDa
LTA	=	Lipoteichoic acid
LDH	=	Lactate dehydrogenase
CXCL12	=	C-X-C motif chemokine ligand 12

CXCR4 = C-X-C motif chemokine receptor 4
COPD = Chronic Obstructive Pulmonary Disease
HBD3 = Human-beta defensin 3
COVID-19 = Coronavirus Disease 2019
VEFG = Vascular endothelial growth factor
MMPs = Matrix metalloproteinases
PDGF = Platelet derived growth factor

CONSENT FOR PUBLICATION

Not Applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Deusenbery, C.; Wang, Y.; Shukla, A. Recent innovations in bacterial infection detection and treatment. *ACS Infect. Dis.,* **2021**, *7*(4), 695-720. http://dx.doi.org/10.1021/acsinfecdis.0c00890 PMID: 33733747
[2] Giuliani, A.; Pirri, G.; Nicoletto, S. Antimicrobial peptides: An overview of a promising class of therapeutics. *Open Life Sci.,* **2007**, *2*(1), 1-33. http://dx.doi.org/10.2478/s11535-007-0010-5
[3] Ganz, T. Defensins: Antimicrobial peptides of innate immunity. *Nat Rev Immunol.,* **2003**, *3*(9), 710-720. http://dx.doi.org/10.1038/nri1180
[4] Durr, UH; Sudheendra, US; Ramamoorthy, A LL-37, the only human member of the cathelicidin family of antimicrobial peptides. *Biochim Biophys Acta.,* **2006**, *1758*(9), 1408-1425.
[5] Bals, R.; Weiner, D.J.; Moscioni, A.D.; Meegalla, R.L.; Wilson, J.M. Augmentation of innate host defense by expression of a cathelicidin antimicrobial peptide. *Infect. Immun.,* **1999**, *67*(11), 6084-6089. http://dx.doi.org/10.1128/IAI.67.11.6084-6089.1999 PMID: 10531270
[6] Shannon, A.H.; Adelman, S.A.; Hisey, E.A.; Potnis, S.S.; Rozo, V.; Yung, M.W.; Li, J.Y.; Murphy, C.J.; Thomasy, S.M.; Leonard, B.C. Antimicrobial peptide expression at the ocular surface and their therapeutic use in the treatment of microbial keratitis. *Front. Microbiol.,* **2022**, *13*, 857735. http://dx.doi.org/10.3389/fmicb.2022.857735 PMID: 35722307
[7] Lee, P.H.A.; Ohtake, T.; Zaiou, M.; Murakami, M.; Rudisill, J.A.; Lin, K.H.; Gallo, R.L. Expression of an additional cathelicidin antimicrobial peptide protects against bacterial skin infection. *Proc. Natl. Acad. Sci.,* **2005**, *102*(10), 3750-3755. http://dx.doi.org/10.1073/pnas.0500268102 PMID: 15728389
[8] Kang, R.; Chen, R.; Zhang, Q.; Hou, W.; Wu, S.; Cao, L.; Huang, J.; Yu, Y.; Fan, X.; Yan, Z.; Sun, X.; Wang, H.; Wang, Q.; Tsung, A.; Billiar, T.R.; Zeh, H.J., III; Lotze, M.T.; Tang, D. HMGB1 in health and disease. *Mol. Aspects Med.,* **2014**, *40*, 1-116. http://dx.doi.org/10.1016/j.mam.2014.05.001 PMID: 25010388
[9] Yu, Y.; Tang, D.; Kang, R. Oxidative stress-mediated HMGB1 biology. *Front. Physiol.,* **2015**, *6*, 93. http://dx.doi.org/10.3389/fphys.2015.00093 PMID: 25904867
[10] Shibusawa, K.; Murakami, T.; Yomogida, S.; Tamura, H.; Nagaoka, I. Antimicrobial cathelicidin peptide CAP11 suppresses HMGB1 release from lipopolysaccharide-stimulated mononuclear phagocytes *via* the prevention of necrotic cell death. *Int. J. Mol. Med.,* **2009**, *23*(3), 341-346. PMID: 19212652
[11] Murakami, T.; Obata, T.; Kuwahara-Arai, K.; Tamura, H.; Hiramatsu, K.; Nagaoka, I. Antimicrobial cathelicidin polypeptide CAP11 suppresses the production and release of septic mediators in D-galactosamine-sensitized endotoxin shock mice. *Int. Immunol.,* **2009**, *21*(8), 905-912. http://dx.doi.org/10.1093/intimm/dxp057 PMID: 19556302
[12] Prasad, S.V.; Fiedoruk, K.; Daniluk, T.; Piktel, E.; Bucki, R. Expression and function of host defense peptides at inflammation sites. *Int. J. Mol. Sci.,* **2019**, *21*(1), 104. http://dx.doi.org/10.3390/ijms21010104 PMID: 31877866
[13] De Smet, K.; Contreras, R. Human antimicrobial peptides: Defensins, cathelicidins and histatins. *Biotechnol. Lett.,* **2005**, *27*(18), 1337-1347. http://dx.doi.org/10.1007/s10529-005-0936-5 PMID: 16215847
[14] Steinmann, J. *Induction and regulation of CAMP gene expression. Department of Biology*; University of Iceland: Reykjavík, Iceland, **2008**.
[15] Khurshid, Z.; Najeeb, S.; Mali, M.; Moin, S.F.; Raza, S.Q.; Zohaib, S.; Sefat, F.; Zafar, M.S. Histatin peptides: Pharmacological functions and their applications in dentistry. *Saudi Pharm. J.,* **2017**, *25*(1), 25-31. http://dx.doi.org/10.1016/j.jsps.2016.04.027 PMID: 28223859
[16] Zanetti, M; Gennaro, R. Cathelicidins: A novel protein family with a common proregion and a variable C-terminal antimicrobial domain. *FEBS Lett.,* **1995**, *374*, 1-5.
[17] Huang, H.J.; Ross, C.R.; Blecha, F. Chemoattractant properties of PR-39, a neutrophil antibacterial peptide. *J. Leukoc. Biol.,* **1997**, *61*(5), 624-629. http://dx.doi.org/10.1002/jlb.61.5.624 PMID: 9129212
[18] Scott, M.G.; Hancock, R.E. Cationic antimicrobial peptides and their multifunctional role in the immune system. *Crit. Rev. Immunol.,* **2000**, *20*(5), 407-431. PMID: 11145218
[19] Liu, Y.J. Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. *Cell,* **2001**, *106*(3), 259-262. http://dx.doi.org/10.1016/S0092-8674(01)00456-1 PMID: 11509173
[20] Yang, D.; Chen, Q.; Chertov, O.; Oppenheim, J.J. Human neutrophil defensins selectively chemoattract naive T and immature dendritic cells. *J. Leukoc. Biol.,* **2000**, *68*(1), 9-14. http://dx.doi.org/10.1189/jlb.68.1.9 PMID: 10914484
[21] Tani, K.; Murphy, W.J.; Chertov, O.; Salcedo, R.; Koh, C.Y.; Utsunomiya, I.; Funakoshi, S.; Asai, O.; Herrmann, S.H.; Wang, J.M.; Kwak, L.W.; Oppenheim, J.J. Defensins act as potent adjuvants that promote cellular and humoral immune responses in mice to a lymphoma idiotype and carrier antigens. *Int. Immunol.,* **2000**, *12*(5), 691-700. http://dx.doi.org/10.1093/intimm/12.5.691 PMID: 10784615
[22] Niyonsaba, F.; Someya, A.; Hirata, M.; Ogawa, H.; Nagaoka, I. Evaluation of the effects of peptide antibiotics human β-defensins-1/-2 and LL-37 on histamine release and prostaglandin D_2 production from mast cells. *Eur. J. Immunol.,* **2001**, *31*(4), 1066-1075. http://dx.doi.org/10.1002/1521-4141(200104)31:4<1066::AID-IMMU1066>3.0.CO;2-# PMID: 11298331
[23] Yang, D.; Chertov, O.; Bykovskaia, S.N.; Chen, Q.; Buffo, M.J.; Shogan, J.; Anderson, M.; Schröder, J.M.; Wang, J.M.; Howard, O.M.Z.; Oppenheim, J.J. Beta-defensins: Linking innate and adaptive immunity through dendritic and T cell CCR6. *Science,* **1999**, *286*(5439), 525-528. http://dx.doi.org/10.1126/science.286.5439.525 PMID: 10521347
[24] Biragyn, A.; Ruffini, P.A.; Leifer, C.A.; Klyushnenkova, E.; Shakhov, A.; Chertov, O.; Shirakawa, A.K.; Farber, J.M.; Segal,

D.M.; Oppenheim, J.J.; Kwak, L.W. Toll-like receptor 4-dependent activation of dendritic cells by beta-defensin 2. *Science,* **2002**, *298*(5595), 1025-1029.
http://dx.doi.org/10.1126/science.1075565 PMID: 12411706

[25] Tran, D.; Tran, P.; Roberts, K.; Ösapay, G.; Schaal, J.; Ouellette, A.; Selsted, M.E. Microbicidal properties and cytocidal selectivity of rhesus macaque theta defensins. *Antimicrob. Agents Chemother.,* **2008**, *52*(3), 944-953.
http://dx.doi.org/10.1128/AAC.01090-07 PMID: 18160518

[26] Tongaonkar, P.; Trinh, K.K.; Schaal, J.B.; Tran, D.; Gulko, P.S.; Ouellette, A.J.; Selsted, M.E. Rhesus macaque θ-defensin RTD-1 inhibits proinflammatory cytokine secretion and gene expression by inhibiting the activation of NF-κB and MAPK pathways. *J. Leukoc. Biol.,* **2015**, *98*(6), 1061-1070.
http://dx.doi.org/10.1189/jlb.3A0315-102R PMID: 26269197

[27] Du, H.; Puri, S.; McCall, A.; Norris, H.L.; Russo, T.; Edgerton, M. Human salivary protein histatin 5 has potent bactericidal activity against ESKAPE pathogens. *Front. Cell. Infect. Microbiol.,* **2017**, *7*, 41.
http://dx.doi.org/10.3389/fcimb.2017.00041 PMID: 28261570

[28] Ikonomova, S.P.; Taaheri, M.P.; Wang, Y.; Doolin, M.T.; Stroka, K.M.; Hube, B.; Karlsson, A.J. Effects of histatin 5 modifications on antifungal activity and kinetics of proteolysis. *Protein Sci.,* **2020**, *29*(2), 480-493.
http://dx.doi.org/10.1002/pro.3767 PMID: 31675138

[29] Travis, SM; Anderson, NN; Forsyth, WR; Espiritu, C; Conway, BD; Greenberg, EP Bactericidal activity of mammalian cathelicidin-derived peptides. *Infect Immun.,* **2000**, *68*(5), 2748-2755.
http://dx.doi.org/10.1128/IAI.68.5.2748-2755.2000

[30] Niyonsaba, F.; Iwabuchi, K.; Someya, A.; Hirata, M.; Matsuda, H.; Ogawa, H.; Nagaoka, I. A cathelicidin family of human antibacterial peptide LL-37 induces mast cell chemotaxis. *Immunology,* **2002**, *106*(1), 20-26.
http://dx.doi.org/10.1046/j.1365-2567.2002.01398.x PMID: 11972628

[31] Heilborn, JD; Nilsson, MF; Kratz, G; Weber, G; Sorensen, O; Borregaard, N The cathelicidin anti-microbial peptide LL-37 is involved in re-epithelialization of human skin wounds and is lacking in chronic ulcer epithelium. *J Invest Dermatol,* **2003**, *120*(3), 379-389.

[32] Davidson, DJ; Currie, AJ; Reid, GS; Bowdish, DM; MacDonald, KL; Ma, RC The cationic antimicrobial peptide LL-37 modulates dendritic cell differentiation and dendritic cell-induced T cell polarization. *J Immunol.,* **2004**, *172*(2), 1146-1156.

[33] Shin, D.M.; Jo, E.K. Antimicrobial peptides in innate immunity against mycobacteria. *Immune Netw.,* **2011**, *11*(5), 245-252.
http://dx.doi.org/10.4110/in.2011.11.5.245 PMID: 22194707

[34] Brogden, KA Antimicrobial peptides: Pore formers or metabolic inhibitors in bacteria? *Nat Rev Microbiol.,* **2005**, *3*(3), 238-250.
http://dx.doi.org/10.1038/nrmicro1098

[35] Li, L.C.; Gao, J.; Li, J. Emerging role of HMGB 1 in fibrotic diseases. *J. Cell. Mol. Med.,* **2014**, *18*(12), 2331-2339.
http://dx.doi.org/10.1111/jcmm.12419 PMID: 25284457

[36] Stros, M.; Polanská, E.; Struncová, S.; Pospísilová, S. HMGB1 and HMGB2 proteins up-regulate cellular expression of human topoisomerase II. *Nucleic Acids Res.,* **2009**, *37*(7), 2070-2086.
http://dx.doi.org/10.1093/nar/gkp067 PMID: 19223331

[37] Kawahara, K.; Hashiguchi, T.; Masuda, K.; Saniabadi, A.R.; Kikuchi, K.; Tancharoen, S.; Ito, T.; Miura, N.; Morimoto, Y.; Biswas, K.K.; Nawa, Y.; Meng, X.; Oyama, Y.; Takenouchi, K.; Shrestha, B.; Sameshima, H.; Shimizu, T.; Adachi, T.; Adachi, M.; Maruyama, I. Mechanism of HMGB1 release inhibition from RAW264.7 cells by oleanolic acid in Prunus mume Sieb. et Zucc. *Int. J. Mol. Med.,* **2009**, *23*(5), 615-620.
PMID: 19360320

[38] Das, N.; Dewan, V.; Grace, P.M.; Gunn, R.J.; Tamura, R.; Tzarum, N.; Watkins, L.R.; Wilson, I.A.; Yin, H. HMGB1 activates proinflammatory signaling *via* TLR5 leading to allodynia. *Cell Rep.,* **2016**, *17*(4), 1128-1140.
http://dx.doi.org/10.1016/j.celrep.2016.09.076 PMID: 27760316

[39] Lee, S.A.; Kwak, M.S.; Kim, S.; Shin, J.S. The role of high mobility group box 1 in innate immunity. *Yonsei Med. J.,* **2014**, *55*(5), 1165-1176.
http://dx.doi.org/10.3349/ymj.2014.55.5.1165 PMID: 25048472

[40] Handayani, IH; Mochammad, H; Novarina, KV; Febriza, AA; Fahirah, SAA Molecular impact on high motility group box-1 (HMGB-1) in pamps and damp. *Indian J Public Heal Res Dev.,* **2019**, *10*(8), 1109.

[41] Bianchi, M.E.; Manfredi, A.A. High-mobility group box 1 (HMGB1) protein at the crossroads between innate and adaptive immunity. *Immunol. Rev.,* **2007**, *220*(1), 35-46.
http://dx.doi.org/10.1111/j.1600-065X.2007.00574.x PMID: 17979838

[42] Scaffidi, P.; Misteli, T.; Bianchi, M.E. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature,* **2002**, *418*(6894), 191-195.
http://dx.doi.org/10.1038/nature00858 PMID: 12110890

[43] Venereau, E.; Casalgrandi, M.; Schiraldi, M.; Antoine, D.J.; Cattaneo, A.; De Marchis, F.; Liu, J.; Antonelli, A.; Preti, A.; Raeli, L.; Shams, S.S.; Yang, H.; Varani, L.; Andersson, U.; Tracey, K.J.; Bachi, A.; Uguccioni, M.; Bianchi, M.E. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. *J. Exp. Med.,* **2012**, *209*(9), 1519-1528.
http://dx.doi.org/10.1084/jem.20120189 PMID: 22869893

[44] Roh, J.S.; Sohn, D.H. Damage-associated molecular patterns in inflammatory diseases. *Immune Netw.,* **2018**, *18*(4), e27.
http://dx.doi.org/10.4110/in.2018.18.e27 PMID: 30181915

[45] Qu, Y.; Zhan, Y.; Yang, S.; Ren, S.; Qiu, X.; Rehamn, Z.U.; Tan, L.; Sun, Y.; Meng, C.; Song, C.; Yu, S.; Ding, C. Newcastle disease virus infection triggers HMGB1 release to promote the inflammatory response. *Virology,* **2018**, *525*, 19-31.
http://dx.doi.org/10.1016/j.virol.2018.09.001 PMID: 30216776

[46] O'Connor, K.A.; Hansen, M.K.; Pugh, R.C.; Deak, M.M.; Biedenkapp, J.C.; Milligan, E.D.; Johnson, J.D.; Wang, H.; Maier, S.F.; Tracey, K.J.; Watkins, L.R. Further characterization of high mobility group box 1 (HMGB1) as a proinflammatory cytokine: Central nervous system effects. *Cytokine,* **2003**, *24*(6), 254-265.
http://dx.doi.org/10.1016/j.cyto.2003.08.001 PMID: 14609567

[47] Kim, S.Y.; Koh, W.J.; Park, H.Y.; Jeon, K.; Lee, S.Y.; Yim, J.J.; Shin, S.J. Down-regulation of serum high-mobility group box 1 protein in patients with pulmonary tuberculosis and nontuberculous mycobacterial lung disease. *Tuberc. Respir. Dis.,* **2017**, *80*(2), 153-158.
http://dx.doi.org/10.4046/trd.2017.80.2.153 PMID: 28416955

[48] Wang, H.; Bloom, O.; Zhang, M.; Vishnubhakat, J.M.; Ombrellino, M.; Che, J.; Frazier, A.; Yang, H.; Ivanova, S.; Borovikova, L.; Manogue, K.R.; Faist, E.; Abraham, E.; Andersson, J.; Andersson, U.; Molina, P.E.; Abumrad, N.N.; Sama, A.; Tracey, K.J. HMG-1 as a late mediator of endotoxin lethality in mice. *Science,* **1999**, *285*(5425), 248-251.
http://dx.doi.org/10.1126/science.285.5425.248 PMID: 10398600

[49] van Zoelen, M.A.D.; Laterre, P.F.; van Veen, S.Q.; van Till, J.W.O.; Wittebole, X.; Bresser, P.; Tanck, M.W.; Dugernier, T.; Ishizaka, A.; Boermeester, M.A.; van der Poll, T. Systemic and local high mobility group box 1 concentrations during severe infection. *Crit. Care Med.,* **2007**, *35*(12), 2799-2804.
http://dx.doi.org/10.1097/01.CCM.0000287588.69000.97 PMID: 17901841

[50] Gaïni, S.; Koldkjær, O.G.; Møller, H.J.; Pedersen, C.; Pedersen, S.S. A comparison of high-mobility group-box 1 protein, lipopolysaccharide-binding protein and procalcitonin in severe community-acquired infections and bacteraemia: A prospective study. *Crit. Care,* **2007**, *11*(4), R76.
http://dx.doi.org/10.1186/cc5967 PMID: 17625012

[51] Angus, D.C.; Yang, L.; Kong, L.; Kellum, J.A.; Delude, R.L.; Tracey, K.J.; Weissfeld, L. Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis. *Crit. Care Med.,* **2007**, *35*(4),

1061-1067.
http://dx.doi.org/10.1097/01.CCM.0000259534.68873.2A PMID: 17334246

[52] Pouwels, S.D.; Hesse, L.; Wu, X.; Allam, V.S.R.R.; van Oldeniel, D.; Bhiekharie, L.J.; Phipps, S.; Oliver, B.G.; Gosens, R.; Sukkar, M.B.; Heijink, I.H. LL-37 and HMGB1 induce alveolar damage and reduce lung tissue regeneration *via* RAGE. *Am. J. Physiol. Lung Cell. Mol. Physiol.,* **2021**, *321*(4), L641-L652.
http://dx.doi.org/10.1152/ajplung.00138.2021 PMID: 34405719

[53] Hosoda, H.; Nakamura, K.; Hu, Z.; Tamura, H.; Reich, J.; Kuwahara-Arai, K.; Iba, T.; Tabe, Y.; Nagaoaka, I. Antimicrobial cathelicidin peptide LL-37 induces NET formation and suppresses the inflammatory response in a mouse septic model. *Mol. Med. Rep.,* **2017**, *16*(4), 5618-5626.
http://dx.doi.org/10.3892/mmr.2017.7267 PMID: 28849130

[54] Roundy, L.M.; Jia, W.; Zhang, J.; Ye, X.; Prestwich, G.D.; OottamasathienQ, S. LL-37 induced cystitis and the receptor for advanced glycation end-products (RAGE) pathway. *Adv. Biosci. Biotechnol.,* **2013**, *4*(8), 1-8.
http://dx.doi.org/10.4236/abb.2013.48A2001 PMID: 24883227

[55] Pouwels, S.D.; Nawijn, M.C.; Bathoorn, E.; Brilman, R.A.; van Oosterhout, A.J.M.; Kerstjens, H.A.M. Increased serum levels of LL37, HMGB1 and S100A9 during exacerbation in COPD patients. *Eur Respir J,* **2015**, *45*(5), 1482-1485.

[56] Schmidt, A.F.; Kannan, P.S.; Kemp, M.W.; Kramer, B.W.; Newnham, J.P.; Jobe, A.H.; Kallapur, S.G. Intra-amniotic LPS modulates expression of antimicrobial peptides in the fetal sheep lung. *Pediatr. Res.,* **2014**, *76*(5), 441-447.
http://dx.doi.org/10.1038/pr.2014.113 PMID: 25105257

[57] Ruiz, T.J.; Aguilar, A.A.; Aguirre, N.M.; Fragoso, P.A.; Vázquez, C.D.A.; Montero, M.J.L.; Domínguez, M.N.R.; Llorente, L.; Carmona, A.B.; Luna, L.J.; Álvarez, N.C.; Vega, J.G.; Sánchez, M.D.; Gilsoul, H.T.; Rodríguez, T.M.; Martín, G.D. Neutrophil extracellular traps contribute to COVID-19 hyperinflammation and humoral autoimmunity. *Cells,* **2021**, *10*(10), 2545.
http://dx.doi.org/10.3390/cells10102545 PMID: 34685525

[58] Chen, L.; Sun, X.; Zhong, X. Role of RAGE and its ligand HMGB1 in the development of COPD. *Postgrad. Med.,* **2022**, *134*(8), 763-775.
http://dx.doi.org/10.1080/00325481.2022.2124087 PMID: 36094155

[59] Denning, N.L.; Aziz, M.; Gurien, S.D.; Wang, P. DAMPs and NETs in sepsis. *Front. Immunol.,* **2019**, *10*, 2536.
http://dx.doi.org/10.3389/fimmu.2019.02536 PMID: 31736963

[60] Oottamasathien, S.; Jia, W.; Roundy, L.M.C.; Zhang, J.; Wang, L.; Ye, X.; Hill, A.C.; Savage, J.; Lee, W.Y.; Hannon, A.M.; Milner, S.; Prestwich, G.D. Physiological relevance of LL-37 induced bladder inflammation and mast cells. *J. Urol.,* **2013**, *190*(S4), 1596-1602.
http://dx.doi.org/10.1016/j.juro.2013.01.002 PMID: 23561390

[61] Mansour, N.A.; Mahmeed, A.A.; Bindayna, K. Effect of HMGB1 and HBD-3 levels in the diagnosis of sepsis- A comparative descriptive study. *Biochem. Biophys. Rep.,* **2023**, *35*, 101511.
http://dx.doi.org/10.1016/j.bbrep.2023.101511 PMID: 37601451

[62] Wulandari, S.; Hartono, W.T. The role of HMGB1 in COVID-19-induced cytokine storm and its potential therapeutic targets. *Rev. Immunol.,* **2023**, *169*(2), 117-131.
http://dx.doi.org/10.1111/imm.13623 PMID: 36571562