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Research Progress of Endotoxin-Induced Acute Lung Injury

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Abstract: Acute lung injury is a common critical condition with complex disease and rapid disease progression, which can lead to acute and severe respiratory impairment and even life-threatening conditions. In the process of acute lung injury caused by endotoxin, the pathogenic factors include direct and indirect damage to the lung. In the pathogenesis, inflammatory response, oxidative stress, iron death and coagulation disorder influence each other, and work together to form a vicious cycle. In order to better understand the pathogenesis of acute lung injury and understand the whole process of the disease, this paper makes a preliminary discussion on the pathogenesis of endotoxin-induced acute lung injury in domestic and foreign journals in recent years, so as to provide a basis for further study of endotoxin-induced acute lung injury.

Acute lung injury is caused by serious infection, shock, trauma, burns, pancreatitis and other non-cardiogenic pathogenic factors, its main pathological features are alveolar epithelial cells and lung capillary endothelial cells injury, cause alveolar-capillary membrane permeability increase, edema, aggravate alveolar injury, alveolar edema, alveolar collapse lead to serious ventilation and blood flow imbalance, causing severe hypoxemia [1].The diagnostic criteria for ALI and ARDS differ slightly. (See Table 1 and Table 2 for details). In addition to the respiratory symptoms such as dyspnea, insufficient blood oxygen, and cough, the severe clinical manifestations of acute lung injury can be further developed into acute respiratory distress syndrome.. Acute respiratory distress syndrome (acute respiratory distress syndrome, ARDS) is a severe progressive state of acute lung

injury, which is a common clinical manifestation, with hypotension, abnormal coagulation function, and diastolic shock, which can occur as high as 40%. According to the incomplete statistics of various hospitals in Shanghai, Beijing and Anhui, the case fatality rate of ALI and ARDS was as high as 40-60% [2].(See Figure 1).

Table 1. Diagnostic criteria for ALI

①	sudden onset
②	Positive chest radioography showed invasive shadows in both lungs
③	Hypoxemia, PaO2/FiO2≤300mmHg
④	pulmonary artery wedge pressure(PAWP)≤18mmHg, or except for cardiogenic factors
⑤	It has a high-risk factor for morbidity

Table 2. Diagnostic criteria for ARDS

	1994	2011
①	Hypoxemia, PaO2/FiO2≤200mmHg	Mild patients(200mmHg<PaO2/FiO2≤300mmHg)
		Moderate patients(100mmHg<PaO2/FiO2≤200mmHg)
		Patient in critical condition(PaO2/FiO2≤100mmHg)
②	The remaining diagnostic criteria were the same as for acute lung injury	

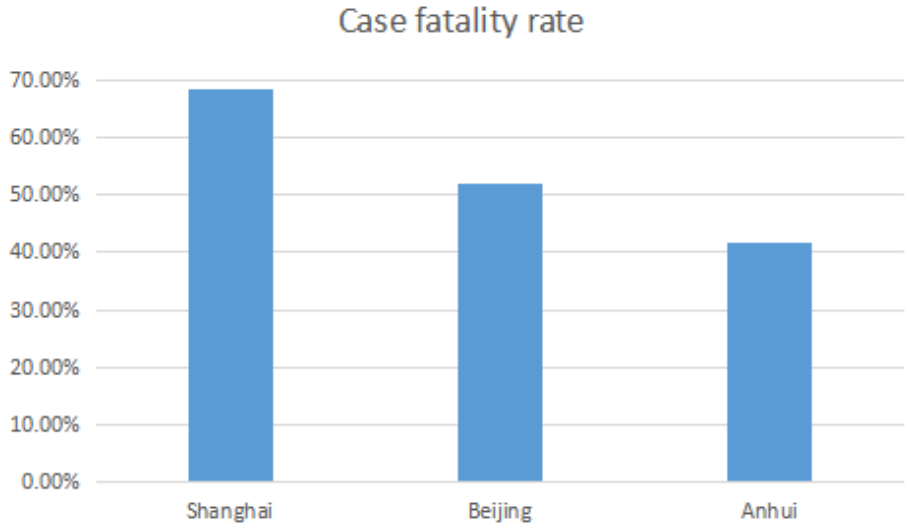

Figure 1. Case fatality rate of ALI and ARDS (incomplete statistics)

1. Inflammatory Response

In the animal model establishment of acute lung injury, acute lung injury induced by sepsis, represented by lipopolysaccharide was the most prevalent. Endotoxin lipopolysaccharide molecule, a key component of the cell wall of Gram-negative bacteria, consists of bacterial body-specific

polysaccharide, nonspecific core polysaccharide, and lipid A. The main toxic component is lipid A, which can cause severe lung injury pathologically characterized by significant pulmonary microvascular damage. The human body is extremely sensitive to bacterial endotoxin. After entering the body, the endotoxin is first recognized by the lipopolysaccharide-binding protein (lipopolysaccharide-binding protein, LBP), which (LBP) transports the endotoxin to the membrane surface differentiation cluster 14 (CD14) protein of immune cells. Subsequently, CD14 carries the endotoxin outside of the cell and is recognized by myeloid differentiation protein 2 (medullary differentiation protein, MD2), which is a special exocrine protein that helps Toll-like receptor 4 recognize lipopolysaccharide endotoxin. Finally, LPS endotoxin binds with Toll-like receptor 4 (toll like receptor-4, TLR 4) to form a new receptor complex, LPS / LBP / CD14.

The process of the new receptor complex activating inflammatory cells to release a large number of inflammatory factors through signal transduction pathways is intricate and has not been fully understood so far. Most studies have shown that the new receptor complex can stimulate the transcription factor nuclear factor- κ B (nuclear factor- κ B, NF- κ B) through cohesion protein 88 (My88), and existing studies consider NF- κ B as the key factor [3] in this inflammatory response.NF- κ B can traverse the nuclear membrane, Binding to specific regions on the chromosome, Enabling the expression of certain recessive genes, Activating the immune cells, Mediates the expression of a large number of proinflammatory genes, Produce a wide variety of diverse cytokines, Such as polymorphonuclear white blood cells (polymorphonuclear, PMN), IL-1 β, interleukins-6 (interleukin-6, IL-6), tumor necrosis factor- α (tumor necrosis factor- α, TNF- α) macrophage inflammatory protein-1 β (macrophage inflammatory protein-1 β, MIP-1 β), interleukin-10 (interleukin-10, IL-10) and so on [4, 5].These proinflammatory factors and anti-inflammatory factors expression and imbalance, and can also activate other signaling pathways, further promote the expression of inflammatory factors, and even cause inflammatory storm, can damage endothelial cells and epithelial cells, destroy the integrity of cell structure, such as to break the inherent integrity of the alveolar-capillary barrier function, promote the development of pulmonary interstitial edema, directly damage lung tissue, sepsis lung injury occurs [6].(See Figure 2).

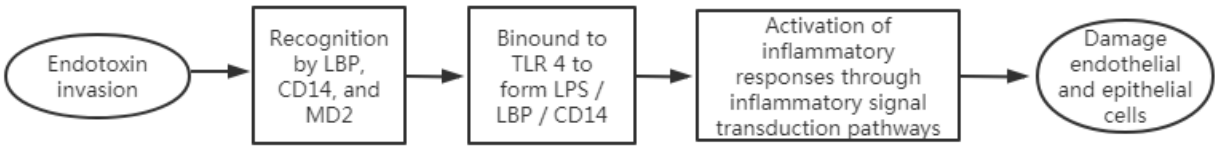

Figure 2. The ALI inflammatory response process

2. Oxidative Stress

There are two major systems of oxidation and anti-oxidation in the body, and the two systems co-exist in the body and both restrict and depend on each other. When the oxidation system is strengthened or the anti-oxidation system is weakened, it will show the state of oxidative stress: ① The oxidation system is mainly active free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). ② The antioxidant system includes antioxidant enzymes: superoxide dismutase (SOD), catalase, glutathione transferase (GST), heme oxygenase 1 (HO-1), glutathione Reductase (GR) and glutathione peroxidase (GSH-PX), etc. Oxidative stress affects the transcription and expression of various genes in the body, and participates in the regulation of life processes such as inflammation, immunity, reproduction, development, and metabolism in the body.

The toxins and metabolites secreted by lipopolysaccharide can change the oxidative state of the cells in the body, and when the degree and scope of damage exceeds its repair capacity, oxidative stress will be induced in the body when the levels of oxidation and anti-oxidation are out of balance.

The action mechanism of oxidative stress in acute lung injury is mainly in the following aspects: ①The ROS of oxidation system is the free radical state of oxygen, mainly including O2-, H2O2, OH, etc, which will attack the biofilm and subcellular structure, and can play a role of excessive oxidation for the body or organs, resulting in the destruction of tissue structure and function of [7]. In addition, studies have shown that ROS can also increase mitochondrial membrane permeability, activate Caspase 9 (cysteine protease 9), promote the release of proapoptotic factors to make tissue cell apoptosis, promote cytotoxicity to cause DNA damage and tissue cell death [8]. ② The relative weakening of the antioxidant system, unable to play the role of the antioxidant and the removal of oxidized substances. In the physiological conditions, Nrf2 binds to Keap1 in the cytoplasm and is in an inhibited state, while ARE binds to Maf-S in the nucleus and is in an inactive state.Nrf2 can protect the body of mice from LPS-induced ALI through anti-inflammatory and antioxidant functions: on the one hand, Nrf2 can resist inflammatory stimuli and inhibit inflammatory damage to cell tissues. On the other hand, Nrf2 is the core molecule of oxidative stress resistance, which is the upstream of superoxide dismutase (SOD), glutathione peroxidase (GSH), glutathione transferase (GST) and other antioxidant enzyme genes, and plays the role of a sensor. When oxidation and antioxidant system are in balance, extracellular oxidants stimulate Nrf2 phosphorylation or Keap 1-SH group modification to promote the dissociation of Nrf2 from Keap 1 protein, and then activate the translocation into the nucleus to bind to the ARE. Nrf2 enters the nucleus to start the transcription of antioxidant enzymes (GSH, SOD) and antioxidant genes, and start the transcription and translation of multiple downstream antioxidant genes and detoxification enzymes, to maintain the cell oxidation-antioxidant balance and inhibit cell inflammation and apoptosis [9]. In addition, HO-1 is a downstream protein of the nuclear transcription factor E2-related factor 2 (Nrf 2) signaling pathway, and HO-1 is one of the most important genes regulated by Nrf 2, which also plays an important anti-inflammatory and anti-oxidant regulatory role in cells [10, 11].(See Figure 3).

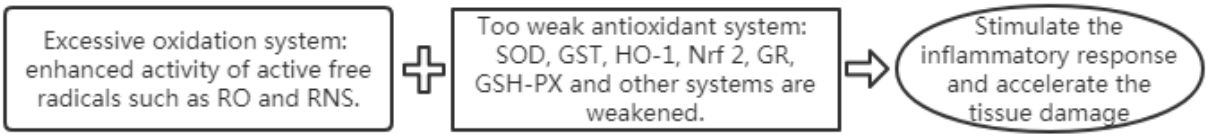

Figure 3. Overview of oxidative stress damage

3. About Other

Iron death: Iron death is a type of cell death caused by the accumulation of iron-dependent lipid peroxides (lipid peroxides, LPO). In response to oxidative stress, massive damage of cellular Fe2 + overload, massive ROS production, and glutathione (GSH) and glutathione peroxidase 4 (glutathione peroxidase 4, GPX 4) can lead to a reduction in the body's ability to remove lipid peroxides, and then induce iron death of [12, 13].

Abnormal coagulation pathway: the inflammatory response caused by the invasion of lipopolysaccharide endotoxin not only leads to tissue damage and the destruction of the endothelial barrier, but also interacts with the coagulation function, leading to the runaway of the coagulation system, promoting the activation of platelets, the inhibition of fibrinolysis, and the release of tissue

factor (TF). Under the premise that inflammatory mediators or cells cause vascular damage,further activation of the exogenous coagulation pathway and secretion of thrombin, inhibit fibrinolysis and promoting fibrous proliferation, thus leading to microcirculation disorders, thrombosis, and aggravating lung injury [14, 15].

4. Summary

The discussion in this paper focuses on inflammatory response and oxidative stress. Oxidative stress is an important factor leading to the exacerbation of the body's inflammatory response and the further progression and aggravation of lung injury. This is also one of the reasons why the clinical efficacy of antibiotics alone in the treatment of pneumonia is not satisfactory. In addition, ferroptosis and abnormal coagulation function of the whole body can also accelerate the development of the disease and cause a cascade expansion effect of systemic inflammatory response, leading to immune dysfunction and aggravated lung injury. (See Figure 4).

The prognosis of acute lung injury caused by endotoxin is poor. Although the medical community has made some progress in its pathogenesis, there is still no stable animal model that can completely simulate the pathological process of human acute lung injury. Therefore, it is still necessary to carry out in-depth research and verification in order to serve the clinic and provide more treatment options to reduce the mortality rate.

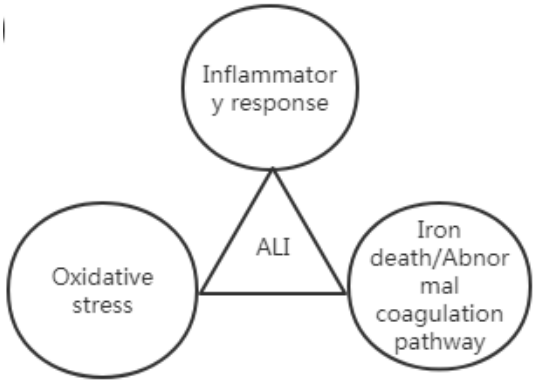

Figure 4. The pathogenesis of ALI

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There is no fund for this thesis.

Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

References

[1] Shi, H. And Ren, C.S. (2013) Basic and clinical research progress of acute lung injury/acute respiratory distress syndrome. Chinese Journal of Lung Diseases (Electronic Edition), 6(04):63-68.

[2] Johnson Elizabeth, R. and Matthay Michael, A. (2010) Acute lung injury: epidemiology, pathogenesis, and treatment. Journal of aerosol medicine and pulmonary drug delivery, 23(4). https://doi.org/10.1089/jamp.2009.0775

[3] Tang, J.R., Michaelis, K.A., Nozik-Grayck, E., et al. (2013) The NF-kappaB Inhibitory Proteins IkappaBalpha and IkappaBbeta Mediate Disparate Responses to Inflammation in Fetal Pulmonary Endothelial Cells. J Immunol, 190(6) :2913-2923 . https://doi.org/10.4049/jimmunol.1202670

[4] Fujishima, S. and Aikawa, N. (1995) Neutrophil-mediated tissue injury and its modulation. Intensive Care Med, 21 (3) :277-285. https://doi.org/10.1007/BF01701489

[5] Meng, L., Song, Z., Liu, A., et al. (2021) Effects of lipopolysaccharide-bindingp protein (LBP) single nucleotide polymorphism (SNP) in Infections, inflammatory diseases, metabolic disorders and cancers. Front Immunol, 12: 681810. https://doi.org/10.3389/fimmu.2021.681810

[6] Rebetz, J., Semple, J.W. and Kapur, R. (2018) The pathogenic involvement of neutrophils in acute respiratory distress syndrome and transfusion-related acute lung injury. Transfusion Medicine and Hemotherapy, 45(5):290-298.DOI:10.1159/000492950.

[7] Kocak, H , Oner-Iyido an, Y., Gürd, L. F., et al. (2005) The relation between serum MDA and cystatin C levels in chronic spinal cord injury patients. Clin Biochem, 38 (11) :1034-1037. https://doi.org/10.1016/j.clinbiochem.2005.08.005

[8] Urban, M.V., Rath, T. And Radtke, C. Hydrogen peroxide(H2O2): a review of its use in surgery. -2.

[9] Huang, X.Y. and Liu, Y.L. (2017) Resveratrol activates Nrf2/ARE signaling pathway to reduce inflammation and oxidative stress in rats with myocardial ischemia-reperfusion injury.Chinese Journal of Traditional Chinese Medicine, 35(06):1516-1520. DOI: 10.13193/j.issn.1673-7717.2017.06.04.

[10] Zhang, H.Y., Zhao, B., Wang, Y.H. and Zhang, Y. (2021) Mechanism of Emodin Inhibiting Inflammation and Oxidative Stress by Regulating Nrf2/HO-1 and MAPKs. Chinese Journal of Immunology, 37(09):1063-1068.

[11] Konrad, F.M., Knausberg, U., Hoene, R., et al. (2016) Tissue heme oxygenase-1exerts anti-inflammatory effects on LPS-induced pulmonary inflammation.Mucosal Immunol, 9 (1) :98-111. https://doi.org/10.1038/mi.2015.39

[12] Yin, H., Xu, L. And Porter, N.A. (2011) Free radical lipid peroxidation:mechanisms and analysis. Chem Rev, 111(10):5944-597. https://doi.org/10.1021/cr200084z

[13] Yang, W.S., Sriramaratnam, R., Welsch, M.E., et al. (2014) Regulation of ferroptotic cancer cell death by GPX4.Cell, 156(1-2):317-33. https://doi.org/10.1016/j.cell.2013.12.010

[14] Grover, S.P. and Mackman, N. (2018) Tissue factor:an essential mediator of hemostasis and trigger of thrombosis. Arteriosclerosis,Thrombosis,and Vascular Biology, 38(4):709-725.DOI:10.1161/ATVBA-HA.117.309846.

[15] Graf, C. and Ruf, W. (2018) Tissue factor as a mediator of coagulation and signaling in cancer and chronic inflammation. Thrombosis Research,2018,164:S143-S147.DOI:10.1016/j.thromres. 01.023.