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Advances in the study of cytokine storm mechanisms in pneumonia: An example of IL-6 and IL-33

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Abstract. In the past decades, pneumonia has been plaguing countries around the world, with great implications for medical and public health. Systems pose a serious challenge. Many pneumonia outbreaks have occurred in local areas and even in the world. Since the end of 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has once again attracted the world's attention to viral pneumonia. At present, a large number of basic research, drug development and clinical trials are being carried out for SARS-CoV-2 and COVID-19. However, patients are generally given symptomatic and supportive treatment, antiviral therapy, immunotherapy, glucocorticoid therapy and respiratory support. Therefore, finding new and effective treatment methods based on the pathogenic mechanism of SARS-CoV-2 is still the current practical demand and research focus. This review focuses on the occurrence and development of CS and the immunopathological damage caused by CS in viral pneumonia, especially in severe pneumonia, and summarizes the potential means of treating CS through IL-related pathways. Research found that different viruses cause CS, cytokines involved in the type and severity of differences, therefore, should also be targeted in the treatment strategy. In addition, in addition to focusing on the treatment of CS, in order to better study the pathophysiological mechanism of virus-induced CS and screen intervention drugs efficiently, how to safely and effectively establish cell and animal models of CS and improve the scientific evaluation system are also key issues worthy of attention.

Keywords: Pneumonia, cytokine storm, interleukins.

1. Introduction

Pneumonia is caused by the invasion and overgrowth of pathogens in the lung parenchyma, which exceeds the host's defenses, leading to the development of exudates in the alveolar spaces and the initiation of pneumonia. The development and severity of pneumonia depends largely on the balance between pathogen and host factors.

Pathogenic bacteria enter the body typically through air inhalation and blood invasion, and subsequently spread to nearby sites of infection. Upon reaching the lower respiratory tract, the pathogen will continue to grow and multiply, with consequences such as fibrin exudation and alveolar cell infiltration.

Interleukins (ILs) are a class of cytokines produced and acted upon by a variety of cells. It originally referred to a class of cytokines produced by leukocytes that play a regulatory role in leukocytes. Now, it refers to a class of cytokines whose molecular structure and biological functions have been largely

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clarified and which have important regulatory roles.Hematopoietic and immunoregulatory processes can be carried out by their collaborating and interacting with one another.In addition to mediating inflammatory responses, ILs are crucial for message transmission, immune cell activation and regulation, and the activation, proliferation, and differentiation of T and B cells.

The function of IL is related to the expression and regulation of the immune response. Many factors are involved in this regulation, such as lymphocytes or macrophages. Lymphocyte-derived cytokines and macrophage-derived cytokines are collectively referred to as monofactors, each of which has different biological activities (e.g., activation of macrophages, promotion of T cell proliferation, etc.).

Current studies have found that the IL pathway can mediate Th2 and Thl /Thl7 related inflammatory responses through its receptors and is related to non-specific immune responses in a variety of infectious diseases of the respiratory system. This article will briefly introduce the immunomodulatory mechanism and significance of Inflammation-Related Cytokines and Pathways in respiratory infectious diseases, and review the related research.

2. Pneumonia

The lungs become inflamed when someone has pneumonia, primarily due to damage to the alveoli. Chest pain, fever, coughing up phlegm, and breathing difficulties are common signs of pneumonia. Mild to severe symptoms are possible. Newborns and elderly adults may have unusual symptoms.

2.1. mechanisms of infection in pneumonia

Typically, a lower respiratory tract infection develops from an upper respiratory tract infection that starts with pneumonia.The symptoms of pneumonia not only cause inflammation of the lung tissue, but also result in lung sequestration, a phenomenon in which the alveoli fill up with fluid, preventing the supply of oxygen to the blood.

2.1.1. Mycoplasma pneumoniae (MP). Mycoplasma pneumoniae infection is caused by infection with mycoplasma. The basic pathology was interstitial pneumonia or bronchiolitis. The clinical manifestations were characterized by refractory and severe cough. MP is one of the important pathogens of pneumonia and other respiratory tract infections in childhood. Sporadic infections occur throughout the year, with peak seasons in late autumn and early winter.

Mycoplasma is a kind of extracellular parasitic bacteria, which is between the size of bacteria and viruses. It is the smallest pathogenic microorganism known to be able to live independently.

The pathogenesis of MP is mainly transmitted by droplets. When the pathogen enters the respiratory tract, it tightly binds to the neuraminic acid receptor of respiratory mucosal epithelial cells on the mucosal surface and attaches, resulting in the destruction of mucosal epithelium, which is the main pathogenic mode of MP.

If the neuraminic acid receptors of mucosal epithelial cells were artificially inhibited, the damage of epithelial cells caused by MP would be greatly reduced. At the same time, MP can release some toxic metabolites, such as ammonia, hydrogen peroxide, protease and neurotoxin, which can cause lesions in the corresponding parts.

In addition, MP antigen and some organizations have some common antigenicity, human body after infection can produce corresponding autoantibodies, immune complex formation, and inflammatory mediators, acid hydrolase, neutral proteolytic enzymes and lysosomal enzyme, according to the resistance and release oxygen such as hydrogen peroxide, lead to immune system damage, pulmonary and extrapulmonary clinical symptoms of multiple organ damage.

2.1.2. Viral pneumonia. Viral pneumonia is a disease caused by upper respiratory tract virus infection, which spreads downward and causes lung inflammation, leading to pulmonary gas exchange dysfunction. Viral pneumonia accounts for 25%-50% [1] of non-bacterial pneumonia.The illness is seasonal, primarily manifesting in the winter and spring. Both occasional cases and epidemics may

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experience it. Fever, headache, discomfort throughout the body, dry cough, and pulmonary infiltration were the primary clinical signs.

The pathogenic mechanism of influenza viruses in humans is currently the subject of a comparatively large number of investigations. Hemagglutinin binds to the sialic acid receptor-containing respiratory epithelial cells' cell surface to start the infection process of influenza A and B viruses. Viral DNA is transcribed and duplicated in the nucleus of cells where influenza viruses are internalized through endocytosis. The virus replicates a large number of new viral particles that spread through the respiratory mucosa and infect other cells. Cytokine storms can be induced by influenza virus infection, leading to a systemic inflammatory response, acute respiratory distress syndrome (ARDS), shock, and multi-organ failure.

The study on the pathogenesis of novel coronaviruses (nCoV) infection began in 2013. dipeptidyl peptidase4 (DPP4), also known as CD26, is a functional receptor of nCoV infection on the surface of human respiratory tract cells. The virus binds to this protein and uses it as a "landing point" to attach to cells and then further invade the body [2]. SARS-CoV-2 virus particles cause disease by binding the spike glycoprotein on the surface of the virus particles to a protein on the surface of lung epithelial cells called angiotensin-converting enzyme 2 (ACE2), which subsequently changes its shape and structure. Lead to virus into the cell, and use the cells and the lipid molecules, amino acids and nucleotides of its new virus particles was synthesized by chemical these new virus particles released into the extracellular, using the same way, infection of the surrounding normal cells.

ARDS and the pathogenic alterations caused by COVID-19 are linked. The significant immunological damage in patients' lungs can be partially explained by the over-activation of T cells, which is characterized by an increase in Th17 and high CD8+ T cell cytotoxicity [3]. According to certain research, COVID-19 patients have fewer and depleted T lymphocytes. The reduction of T cells may be directly mediated by cytokines such TNF-α, IL-6, and IL-10 [4].

2.2. Severity of Pneumonia

Pneumonia is a very common disease and is one of the leading causes of death in people of all ages. It affects nearly 450 million people globally each year and causes nearly 4 million deaths, accounting for nearly 7 per cent of global deaths [5,6]. The incidence of pneumonia is higher in children under 5 years of age and in people over 75 years of age. The incidence in developing countries is about five times that in developed countries. The incidence of viral pneumonia is close to 200 million cases. It was pneumonia that was the eighth leading cause of death in the United States in 2009 [7].

In 2008, 151 million pediatric cases were identified in developing countries and 5 million in developed countries, totaling about 156 million children with pneumonia. Pneumonia is the leading cause of child mortality in developing countries. Infancy is the peak period for many of these cases.

3. Cytokine storm and pneumonia

Although pneumonia is caused by pathogens, it has been found that direct pathogen-induced cellular damage is only one of the pathogenic mechanisms. The key factor leading to severe pneumonia and even death is cytokine storm (CS) caused by excessive inflammatory response and dysregulation of immune homeostasis after infection and injury. Therefore, treating pneumonia by modulating the immune response, especially in the prevention and treatment of severe pneumonia, has attracted increasing attention.

3.1. The meaning of CS and the cytokines involved

In the process of immune response, cells interact with each other and constrain each other by secreting cytokines, forming a complex and orderly cytokine regulatory network to maintain the balance and homeostasis of the immune system [8].

However, under some external stimuli, such as severe infection, the excessive inflammatory response breaks this balance, and the body overproduces a variety of cytokines in a short time, leading to the occurrence of CS and systemic inflammatory response syndrome, leading to serious tissue and organ

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damage. Therefore, CS, also known as cytokine release syndrome (CRS), is commonly seen in immune-related diseases or after immunotherapy, such as graft-versus-host disease, severe viral infections, and chimeric antigen receptor T (CAR-T) cell therapy.

Cytokines involved in CS are varied, depending on the structure and function, mainly divides into the interferon (IFN), interleukin (IL), chemotactic factor (chemokine), colony stimulating factor (CSF), tumor necrosis factor (TNF), growth factors (GF) six categories. Interleukins related cytokines will be discussed in the following paragraphs.

3.1.1. Mechanisms of severe pneumonia caused by CS. Consider viral pneumonia as an example. When CS arises, different cytokine-mediated signals are greatly intensified, resulting in aberrant and disorganized immunological and inflammatory responses that cause significant immunopathological harm to lung tissue. Acute lung injury (ALI) occurs in patients, and in severe cases, it rapidly progresses to acute respiratory distress syndrome (ARDS) and even multiple organ dysfunction syndrome (MODS). The exact mechanism of its occurrence is not clear, but several factors may play a key role. First, massive and rapid viral replication leads to necrosis of infected cells, release of proinflammatory cytokines, recruitment of inflammatory cell infiltration, and induction of apoptosis of alveolar epithelial cells and pulmonary capillary endothelial cells via Fas/FasL or TRAIL/DR5 pathways [9]. Then, damage-associated molecular patterns (DAMPs) released by cell and tissue damage can further activate macrophages and promote the secretion of chemokines, inducing more neutrophils, monocytes and lymphocytes to gather to the inflammatory site, producing more pro-inflammatory cytokines, and enhancing the level of inflammatory response. In addition, some viruses such as SARS - CoV capable of encoding various structural and non structural protein against interferons early reaction, causing viral replication can not be effectively suppressed, produce a large amount of proinflammatory factor, raise and activate pathogenic inflammatory mononuclear macrophages, induction of T cell apoptosis, and lead to the lack of immune response to negative control signal [10]. Ultra immune response caused by diffuse cell and tissue damage, causing vascular leakage, alveolar edema and alveoli transparent membrane formation, cause pulmonary edema and hypoxia, clinical expression is a cardiac pulmonary edema and stubborn hypoxemia, appear even ARDS.

Excessive inflammatory cytokines and chemokines may overflow into the circulatory system, leading to systemic CS, or severe acid-base and electrolyte disorders and shock due to respiratory and circulatory system failure, eventually leading to MODS. In addition, when the course of disease is long, the infiltration and activation of fibroblasts around blood vessels cause a large amount of fibrin exudation, coupled with uncontrolled epithelial cell proliferation and injury repair, which may lead to the occurrence of pulmonary fibrosis. Thus, the virus induced CS and subsequent immune pathological events caused severe pneumonia in virus infection and even fatal disease plays an important role, inhibition of CS is the key to decrease the rate of severe viral pneumonia and mortality.

3.1.2. Treatment of CS. At present, the intervention strategies for CS caused by various causes are still in the exploratory stage. Most of the previously reported methods are based on the management experience of CS caused by CAR-T therapy. Given that viral infection-induced CS is often accompanied by high viral titers and excessive inflammatory responses, interventions aimed at controlling viral load and reducing inflammatory and immune responses may help to suppress CS and improve patient outcomes. Therefore, drugs with anti-inflammatory or immunomodulatory effects are generally considered to be effective.

It is also an effective strategy to treat CS by targeting some key cytokines in the process of CS and using their monoclonal antibodies and recombinant proteins to antagonize them and block their proinflammatory effects. Such as IL-6 blocker tocilizumab [11], TNF-α inhibitor etanercept [12] and IL-1 antagonist anakinra [13] have been reported to show some efficacy in CS caused by CAR-T therapy.

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3.2. Interleukins

ILs are a group of cytokines (secreted signaling molecules). Expression was first discovered in leukocytes as a means of intercellular signaling. ILs can be produced by a variety of cells. The function of the immune system is largely dependent on interleukins. Some rare interleukin deficiencies often lead to autoimmune diseases or immunodeficiency.

3.2.1. IL-6. The IL-6 gene is located on chromosome 7 and has a molecular mass of 26kDa. IL-6 plays an important role in immune regulation, inflammatory response, hematopoietic regulation and other processes.

The IL-6 receptor system consists of two peptide chains. The α-chain, also known as the specific binding chain, is the IL-6R with a molecular weight of 80kDa. The β-chain, also known as Signal transduction protein, has a molecular weight of 130kDa (gp130). IL-6R and gpl30 both exist as membrane and soluble receptors.IL-6R is composed of 468 amino acids, 6N glycosylation sites. IL-6R alone binds to IL-6 with low affinity. IL-6R is widely distributed, such as activated B cells, myeloma cells, quiescent T cells, monocytes and so on. Because IL-6 can only exert its biological activities and its receptor, given the IL-6's crucial role in many diseases, by adjusting the level of IL-6R to control the expression level of IL-6, has become a possible means for the treatment of related diseases.

As a multifunctional inflammatory cytokine and a crucial part of the inflammatory mediator network, IL-6 plays a significant role in the inflammatory response. When pro-inflammatory or early cytokines are present, their harmful effects can be counterbalanced by anti-inflammatory or long-term cytokines, which has a somewhat protective impact. Because of their dual action as anti-inflammatory and anti-inflammatory, the amount in the tissue affects the effects. While overproduction can result in a variety of inflammatory injuries, normal amounts are advantageous. In vitro lung injury caused by bacterial endotoxin demonstrates how IL-6 inhibits macrophage production of TNF and IL-1, hence exerting cytoprotective and anti-inflammatory effects.

Airway inflammation and structural remodeling are closely related to cytokines released by inflammatory cells. Asthma is a chronic inflammatory disease of the airway characterized by extracellular matrix deposition, inflammation, angiogenesis and airway smooth muscle hyperplasia, which leads to airway wall thickening. Elevated levels of IL-6 have been found in asthma, but its pathological role is not well understood. In the development of asthma, IL-6 may play a bi-directional role of pro-inflammatory and anti-inflammatory, but at what level it plays which role remains to be studied.

3.2.2. IL-33/ST2. The chromosome 9 carries the human IL-33 gene sequence, which is 270 amino acid long and has a molecular weight of 30 kDa. IL-33 mRNA was found to be strongly expressed in mucosal systems (respiratory tract, digestive tract, skin, etc.), the brain, and the spinal cord, and to be lowly expressed in the spleen, lymphatic tissues, pancreas, heart, and kidney in both human and mouse cDNA sequencing analysis [14].

IL-33 is primarily expressed in smooth muscle cells, fibroblasts, endothelial cells, and epithelial cells, among other types of cells. A significant quantity of IL-33 can also be expressed by certain immune cells, including mast cells, dendritic cells, macrophages, and others [15]. IL - receptor of 33 ST2 contains three subtypes: variation ST2 (ST2V), soluble ST2 (sST2), and across-membrane type ST2 (ST2L). These subtypes are expressed in a variety of cells, including mast cells, eosinophils, basophils, dendritic cells, lymphocytes, NK cells, and NKT cells [16]. These cells have a receptor ST2 that IL-33 can bind to. This binding causes the cells to secrete a range of cytokines, including IL-4, IL-5, IL-13, IFN-γ, TNF-α, and IL-2. Consequently, IL-33/ST2 is crucial for a number of inflammatory responses and allergy disorders, particularly for Th2-like immune responses [17].

Numerous investigations have verified that the IL-33/ST2 signaling pathway is crucial for identifying harmful germs that invade the body and triggering defense mechanisms. Numerous studies have demonstrated that pathogenic microorganisms can cause a range of cells to express and secrete IL-33. IL-33 then interacts with target cells' ST2 receptor to trigger the T helper cell (Th) type 2 immune

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response, which in turn mediates diseases linked to lung infections. There was a relationship between the level of infection and IL-33 expression.

Different from most viral infections that initiate the Th1 immune response, respiratory virus infection can stimulate the Th2 immune response. In the mouse model of early respiratory syncytialvirus (RSV) infection, the levels of IL-33 mRNA and protein and the expression of ST2mRNA were significantly increased in the dendritic cells and pulmonary macrophages, and there was a positive correlation between them [18]. In the lung of mice, a significant amount of CD45+ST2+ cells were discovered. After stimulation with recombinant mouse IL-33 in vitro, the expression of IL-13 mRNA in CD45+ST2+ cells was up-regulated, indicating that the IL-33/ST2 signaling pathway can stimulate IL-13 synthesis [19].

When TLR3 or TLR7 agonists were co-cultured in vitro with RSV-infected DCS and pulmonary macrophages, the production of IL-33 mRNA increased. However, when TLR antagonist was co-cultured with RSV-infected DCS and pulmonary macrophages, the production of IL-33 mRNA was drastically reduced. These findings imply that the TLR signaling pathway is necessary for RSV-induced IL-33 expression activation. Following RSV infection, a number of cells are stimulated to produce more IL-33 and ST2 receptors, and the TLR signaling pathway promotes the release of Th2 type cytokines, particularly IL-4, IL-5, IL-10, IL-13, and so on, to cause inflammation in the airways.

4. Conclusion

In conclusion, CS plays an important role in the progression of severe viral pneumonia caused by highly pathogenic respiratory viruses. Inhibiting CS may help to relieve the symptoms of patients, reduce the incidence of severe pneumonia, and improve the prognosis.

This article focuses on the mechanism of viral infection inducing CS, causing immunopathological damage and leading to severe pneumonia. The molecular biological characteristics of IL-6, IL-33 and other interleukins and their roles in inducing immune response were described in detail. It is expected to provide some reference for the treatment of viral pneumonia including COVID-19.

Finally, there are many kinds of cytokines involved in CS, with different structures and functions. Cytokines other than IL also play an important role in CS. There are differences in the types of cytokines involved in CS and the severity of CS induced by different viruses, and related studies still need to be further studied.

The author thinks that, due to the different viruses cause of CS, cytokines involved in the differences in nature, all should also be targeted on the treatment strategy. In addition, in addition to focusing on the treatment of CS, in order to better study the pathophysiological mechanism of virus-induced CS and screen intervention drugs efficiently, how to safely and effectively establish cell and animal models of CS and improve the scientific evaluation system are also key issues worthy of attention.

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