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Mini Review

COVID-19 Associated Inflammatory Pathways

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Introduction

COVID-19 is a new type of human viral disease caused by SARS-CoV-2, which has caused severe damage because of its rapid spread and high mortality. Worldwide, the number of people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 is the pathogenic factor of COVID-19) is increasing rapidly. The primary complications of SARS-CoV-2 infection are severe pulmonary inflammation and acute respiratory distress syndrome [1-4]. The SARS-CoV-2 virus has evolved a variety of tools to evade immune detection and destruction and has become the most powerful virus in more than 100 years. This paper evaluates the latest research on signal transduction pathways related to COVID-19, hoping to provide a reference for the diagnosis and treatment of COVID-19.

IL-33-ST2 Pathway

The latest study found that the alarm protein cytokine interleukin-33 (IL-33) is a key factor driving all stages of COVID-19 disease. IL-33 is a cytokine of the IL-1 family expressed in the barrier tissue and performed multiple functions. After infection and cell injury, IL-33 is released rapidly in the lungs, mainly by damaged epithelial alveolar cells [5]. IL-33 enhances the differentiation of Foxp3+ regulatory T (Treg) cells mediated by TGFβ [6]. It stimulates CD11c+ myeloid dendritic cells to secrete IL-2, which drives Treg cells' expansion, thus promoting inflammation regression. Patients with mild symptoms of SARS-CoV-2 infection tend to have large number of Treg cells and alveolar macrophages showing scavenger decomposition (FABP+) phenotype [7,8]. In the presence of sufficient immune response and virus clearance, IL-33 may promote Treg cell-dependent respiratory tissue homeostasis's rapid recovery, which may cause mild or asymptomatic COVID-19 in most people.

In susceptible people, IL-33 released by damaged lower respiratory tract cells may induce regulatory T cell disorders that express GATA3, which destroys immune tolerance and leads to severe spontaneous lung disease caused by SARS-CoV-2. The condition may initially be maintained by type 2 innate lymphoid cells differentiated by IL-33 and locally expanded γδT cells [9]. In severe COVID-19 cases, IL-33/ST2 signaling may expand the number of T cells expressing pathogenic granulocyte-macrophage colony-stimulating factor, inhibit antiviral interferon response, trigger excessive inflammation and promote thrombosis [9]. In patients with severe COVID-19, IL-33 may drive pulmonary fibrosis by inducing myofibroblasts and epithelial-mesenchymal transition [9]. The serum sST2 in patients with COVID-19 was significantly increased and negatively correlated with the number of CD4+ and CD8+T lymphocytes. During the disease's progression, serum sST2 levels continued to rise in severe cases that did not survive [10]. Recent studies have found that exposure to SARS-CoV-2 peptides causes IL-33 expression in viral serum positive patients. The production of IL-33 is related to T cell activation and the severity of lung disease. The use of monoclonal antibodies (or small molecular inhibitors) to target IL-33/ST2 signaling pathways may prove to be an effective strategy for controlling COVID-19 pandemics.

STAT Pathway

COVID-19 is caused by SARS-CoV-2 infection and has a variety of clinical symptoms. SARS-CoV-2 is a sarcoma virus, and its overall structure is similar to that of SARS-CoV-1. The SARS-CoV-2 genome contains a large 5 'open reading frame (ORF) 1AB, which encodes two polyproteins, including 16 non-structural proteins (NSPs, NSP1-NSP16). The 3' end of the genome encodes a

structural protein S (S, consisting of S1 and S2 subunits, envelope protein (E), membrane protein (M), and nucleocapsid protein (N). Scattered between these genes is ORF, which encodes non-structural helper proteins ORF3a, ORF3b, ORF6, ORF7a, ORF7b, and ORF8 [11,12]. Several SARS-CoV-1 proteins can antagonize the antiviral activity of IFNs and their activation of downstream JAK (Janus kinase)-STAT signal pathway. JAK family kinases (JAK1, JAK2, JAK3, TYK2) have extensive ontogeny functions, immunity, chronic inflammation, fibrosis, and cancer [13]. When type I interferon (IFN-I) production is impaired, severe conditions can lead to ARDS and extensive coagulopathy. COVID-19 is a series of pathophysiological inactivation processes caused by SARS-CoV-2 gene products NSP1 and ORF6 protein. These viral components induce signal transducer and activator of transcription 1 (STAT1) dysfunction and compensatory overactivation of STAT3. In cells infected with SARS-CoV-2, the positive feedback loop established between STAT3 and plasminogen activator inhibitor-1 (PAI-1) may lead to the upgrading of activation cycle, which is the same as the interdependent signal network in COVID-19. Specifically, the upregulation of PAI-1 leads to coagulation disorders characterized by intravascular thrombosis. Overexpressed PAI-1 binds to TLR4 on macrophages to induce the secretion of proinflammatory cytokines and chemokines. Acute lung injury also activates EGFR and leads to STAT3 phosphorylation. Autopsies of COVID-19 patients often showed an increase in (DAD) and hyaluronic acid (HA) production in patients with diffuse alveolar injury, leading to an increase in PAI-1 levels [14]. Severe COVID-19 cases usually depend on the overstimulation of the STAT3/PAI-1 signaling network. This signal may be an Achilles' heel of COVID-19 and a vulnerable spot of the disease. Therefore, the use of STAT therapy may provide a new treatment for this complex disease. Both STAT3 and PAI-1 have been independently involved in cancer development and have been the subject of extensive clinical studies. The common node of STAT3 and PAI-1 activity may also play a role in some pSTAT3 positive cancers, producing a series of harmful reactions similar to COVID-19. Therefore, any STAT-related drugs developed for the treatment of COVID-19 may eventually have a wider clinical use [14].

STING Pathway

STING is a pattern recognition receptor located in the endoplasmic reticulum. When cells are infected with the DNA of bacteria and the DNA viruses (including endogenous retroviruses), the cGAS-STING pathway plays a central role in the perception of cytoplasmic DNA. The inability to express STING in some cell types will contribute to the priority homing of DNA viruses. cGAMP is the main activator of STING and the stimulator of the interferon gene. The STING-TBK1-IRF3 pathway can synthesize interferon. STING is also the hub for activating NF-kappa B and autophagy. IFN α/IFN-β downstream of STING can promote the replication of SARS coronavirus, including SARS-CoV-2, can be observed in mouse models of the SARS-CoV virus MERS-CoV virus [15,16]. Parallel activation of macrophages, dendritic cells, and B cells until depletion may also lead to the excessive triggering of TCR and STING by CD4+, CD8+, and NK cells, resulting in depletion and death, and further transmission of SARS-CoV-2.

STING is the "hub" of the immune response, which drives the TBK1-IRF3 pathway and participates in cell death (including T lymphocyte death). Direct targeting of STING effectively suppresses delayed cytokine storms and prevents lymphopenia, pneumonia and angiopathy than blocking only a single cytokine (such as IL-6). Direct inhibition of delayed overactivation of STING in severe COVID-19 may better prevent premature apoptosis of memory center T cells and early or late recurrence of SARS-CoV-2 infection, and the same results have been observed in young patients [17]. Therefore, drugs that prevent the overactivation of STING can be used to treat COVID-19, including cheap and well-tolerated drugs, such as vitamin D and aspirin [18]. Interestingly, in a large retrospective study conducted in the US ICU, even low-dose aspirin appeared to be reduced by mechanical ventilation, ICU admission, and hospital mortality in hospitalized COVID-19 patients [19]. If this conjecture is confirmed, the findings could significantly impact the future of the COVID-19 pandemic.

IFN-AhR Pathway

The complexity of COVID-19 is that the patient may not have the initial symptoms, but the disease will develop rapidly once the symptoms appear. It is generally believed that uncontrolled inflammation is associated with death [20,21]. The inflammatory pathway targeting key pro-inflammatory cytokines IL-6 or JAK/STAT has been studied in critically ill patients with COVID-19 [22]. Most pro-inflammatory cytokines can damage alveolar epithelium and endothelial cells, leading to capillary permeability and pulmonary fibrinolysis, thus hinder the exchange of oxygen (O2) and carbon dioxide (CO2), and lead to hypoxia, which is the key factor leading to COVID-19's induced death [23]. The autopsy report showed that there was a large amount of gray-white mucous fluid in COVID-19's lungs [24,25]. Protein exudation was also continuously observed in COVID-19 patients diagnosed after lung cancer surgery [26]. In addition, a new single-cell sequencing study reported the expression of mucin in pulmonary epithelial cells of patients with COVID-19 [27]. These observations lead us to assume that SARS-CoV-2 infection may stimulate mucus production, thereby promoting hypoxia by preventing the spread of O2 in the alveoli. In a recent study, the authors found that mucin accumulated in (BALF) in bronchoalveolar lavage fluid (BALF) of COVID-19 patients and up-regulated in the lungs of SARS-CoV-2-infected mice and rhesus monkeys. Induction of interferon (IFN)-β or IFN-γ after SARS-CoV-2 infection results in the activation of aromatics receptor (AhR) signal through an IDO-Kyn-dependent pathway,

which leads to up-regulation of mucus secretion and membrane binding in alveolar epithelial cells. Therefore, the accumulation of alveolar mucus affects the blood-gas barrier, resulting in hypoxia and reduced vital capacity, which can be reversed by blocking AhR activity [28]. The AhR blockade may also be effective against severe influenza, which is worthy of further study.

Concluding Remarks

Due to high prevalence and long incubation period, and usually asymptomatic, severe SARS-CoV-2 has infected millions of people worldwide, leading to a coronavirus disease (COVID-19) pandemic in 2019. Although much is known about the underlying mechanisms of lung pathology in COVID-19, the immune system is the cause of inflammation and cytokine "storms" in the lungs of a large number of patients. Therefore, a better understanding of pulmonary inflammation drivers in COVID-19 may lead to targeted treatments to reduce morbidity and mortality. There are few studies on the potential mechanism of lung pathology in COVID-19. More mechanism studies will be needed to provide sufficient reference for prevention, control, and treatment in the future.

Conflict of Interest

None.

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