Book Chapter

Features of Cytokine Storm Identified by Distinguishing Clinical Manifestations in COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by infection of a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is currently spreading all over the world. In response, we developed a practical model for identifying the features of cytokine storm, which is common in acute infectious diseases and harmful manifestation of COVID-19, by distinguishing major and minor clinical events. This model is particularly suitable for identifying symptoms of COVID-19. Based on this model, features of cytokine storm and pathogenesis of COVID-19 have been proposed to be a consequence of the disequilibrated cytokine network resulting from increased biological activity of transforming growth factor-β (TGF-β), which induces certain clinical manifestations such as fatigue, fever, dry cough, pneumonia, abatement and losing of olfactory and taste senses in some patients. Research and clarification of the pathogenesis of COVID-19 will contribute to precision treatment. Various anti-TGF-β therapies may be explored as potential COVID-19 treatment. This novel model will be helpful in reducing the widespread mortality of COVID-19.

Keywords

Coronavirus Disease 2019 (COVID-19); Clinical Manifestation; Cytokine Storm; Pathogenesis; Transforming Growth Factor-β (TGF-β)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is currently spreading worldwide and contributing to widespread mortality. There is an urgent need to clarify the pathogenic mechanism underlying the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In response, on the basis of our comprehensive clinical experience, profound understanding of cytokine network, and the recognition of the comparative research between Chinese medicine and modern medicine over the past years [1-4], we developed a practical diagnostic model to judge and identify the features of cytokine storm of acute infectious diseases by distinguishing the clinical manifestations of patients. The features of cytokine storm elicited by COVID-19 was clarified as a typical example by using this model.

Clinical Manifestations of COVID-19

The first and main symptoms of COVID-19 are fever, fatigue, dry cough, abatement and losing of olfactory and taste senses in most patients. Patients with severe disease may also experience dyspnea, hypoxemia, shock, and multiple organ failure [5-6]. In the early stage of COVID-19, the total number of white blood cells is normal or decreased, and the number of lymphocytes decreases, with multiple small patch shadows and interstitial lesions on lung CT images. Autopsies on patients with COVID-19 show obvious inflammation of lungs accompanied with a large amount of mucus [7].

The clinical manifestations of COVID-19 can be divided into four categories. (1) The major manifestation: A characteristic and major symptom of COVID-19 is fatigue, with the degree of

fatigue being associated with the clinical type of COVID-19. (2) The minor manifestations: These include fever, dry cough, abatement and losing of olfactory and taste senses, interstitial lung changes, and lymphopenia. The major and minor manifestations are the initial and characteristic manifestations directly caused by the disequilibrated cytokines of COVID-19. (3) The manifestations due to secondary pathogenic processes: Some pathogenic processes may occur in the progression and evolution of COVID-19, which can induce corresponding clinical manifestations. For example, the cough, sputum, and chest distress may be caused by secondary lung bacterial infection. Critical patients may display respiratory failure, shock, and multiple organ failure, as well as blood pressure reduction, poor peripheral perfusion, and others. (4) The manifestations of comorbidities: Comorbidities such as diabetes, hypertension, and coronary heart disease may be enhanced by the infection and progression of COVID-19 [8]. The mixed manifestations make the identification of cytokine storm and true pathogenesis of COVID-19 extremely difficult.

A Practical Diagnostic Model to Identify Cytokines and Clinical Manifestations

In modern medicine, the understanding and recognition of diseases are achieved based on the systematic investigation of etiology, pathogenesis, pathogenic process, clinical manifestations, treatment and rehabilitation. The dysfunction of cytokine network and clinical manifestations of diseases are closely associated with each other and have a causal relationship. Different pathogenesis and disequilibrated cytokine network status will yield different pathological processes, and in return, different manifestations.

Cytokines are a group of polypeptides functioning as the first messenger molecules, and play key roles during the occurrence, development, and evolution of diseases. Clinical manifestations of diseases depend on the leading cytokines which play dominant roles in the disequilibrated cytokine network status.

Based on the causal relationship between cytokines and manifestations, we developed a practical diagnostic model to identify the features of cytokine storm as a result of acute infectious diseases. This model includes the following diagnostic procedures: 1) observing and distinguishing the patient's comprehensive clinical manifestations; 2) differentiating the major, minor, secondary and other manifestations; 3) judging the leading cytokines that display the dominant roles of the disequilibrated cytokine network and eliciting the manifestations of diseases, and; 4) identifying the features of cytokine storm of the diseases. Following this model, the pathogenesis and features of cytokine storm of COVID-19 infection was elucidated in the following.

Features of Cytokine Storm and Pathogenesis of COVID-19Resource Identification Initiative

Abnormal expression and dysfunction of cytokines in diseases can lead to a certain disequilibrated cytokine network and elicit corresponding pathogenic changes and manifestations [9-11]. The disequilibrated cytokine network status of diseases can be divided into three levels: mild, ordinary and critical. Commonly, a critical level of disequilibrated cytokine network status is known as cytokine storm, which means an excessive number and quantity of cytokines are released. Cytokine storm can lead to the production of a number of biological mediators that cause changes to the body and interfere with normal cell function, creating high levels of inflammation in the area of the body being flooded, which can be fatal.

Increasing evidence has shown that a number of cytokines, including interleukins (IL-1, IL-6, IL-8), tumor necrosis factor (TNF), and interferon (IFN) displayed significant changes in COVID-19 patients [12]. However, the features of cytokine storm of COVID-19 have not been well identified because of the complexity of the cytokine network. And few studies have focused on the change and role of transforming growth factor-β (TGF-β) during COVID-19 infection.

Following the above model, we proposed that cytokine storm in COVID-19 was a consequence of disequilibrated cytokine network resulting from increased biological activity of TGF-β. SARS-CoV-2 viruses proliferate and reproduce in their target cells, inducing abnormal stress and immune responses of the body. This process disturbs the normal expression and functional regulation mechanisms of cytokines, finally resulting in disequilibrated cytokine network that dominated by TGF-β and its synergetic factors. TGF-β binds to its corresponding receptors and triggers a series of cascade biochemical reactions, pathological processes and clinical manifestations (Figure 1). TGF-β is a cytokine superfamily and has a broad spectrum of biological activities in the body. As an endogenous pyrogen, TGF-β can cause fever, but its pyrogenicity is relatively weak and usually only results in low fever [13]. Fatigue is a typical symptom of COVID-19, due to mitochondrial dysfunction and decline Na^+-K^+-ATPase activity [14-15]. Dry cough and interstitial lung change are also caused by increased TGF-β, which is a fibroblast growth factor and has been shown to induce interstitial lung change. TGF-β promotes the secretion of bronchial mucus cells, induces large amounts of thick mucus and pulmonary sputum embolism in the lungs, which hinders normal breathing, and may lead to critical complications, such as serious infections and shock. In addition, TGF-β is a strong immunosuppressive factor in the body, significantly suppressing immune function and delaying recovery [16]. Furthermore, TGF-β can inhibit the proliferation and differentiation of lymphocytes [17], reducing the number of peripheral blood lymphocytes. TGF-β has negative impacts on olfactory and gustatory receptor neurons and neurogenesis by inhibiting progenitor cell proliferation and differentiation, elicits the abatement and losing of olfactory and gustatory sense in some patients [18-20]. Overall, the clinical manifestations of COVID-19 are highly consistent with increased TGF-β activity, which is the basic evidence supporting TGF-β as the main player of cytokine storm resulting from SARS-CoV-2 infection.

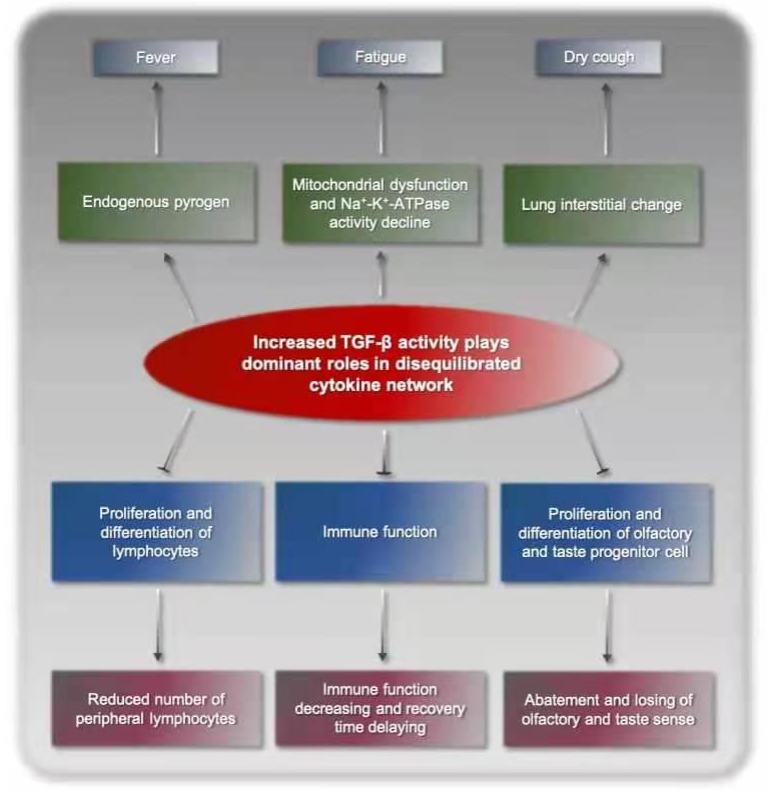

Figure 1: The pathogenic mechanism of COVID-19 manifestations.

Heterogeneity and Discrepancy of COVID-19 Cytokine Storm

COVID-19 patients can be divided into three types: asymptomatic/mild, ordinary, or critical types (Figure 2), which conform with the corresponding levels of mild, moderate and critical cytokine storm, respectively. The different clinical types might be a result of different cytokine storm and different immune response of the body. A basic feature of COVID-19 cytokine storm is an abnormally increased TGF-β activity. However, due to the differences between individuals, different COVID-19 patients and even the same patient at different stages may show inconsistent pathogenesis and clinical manifestations.

In clinical practice, physicians should strive to make a timely identification based on such clinical manifestations. For example, when the disease is mainly characterized by obvious fatigue and low fever, the activity of TGF-β might be dominant. In contrast, when the main manifestation is hyperpyrexia, the activities of IL-1 and TNF-α might be increased and more likely to have the dominant function.

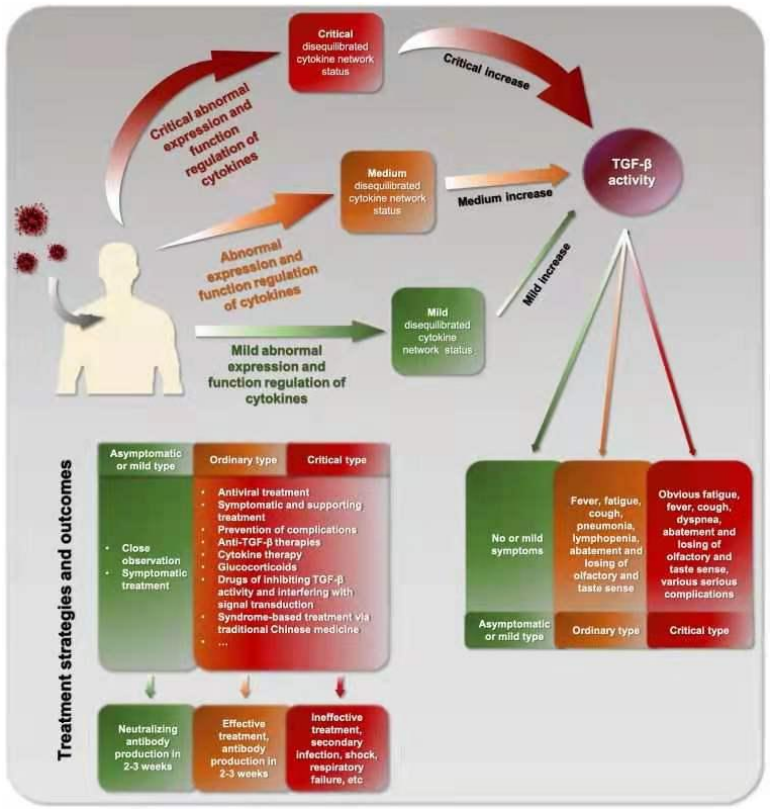

Figure 2: The overall pathogenic process and cytokine storm of COVID-19.

By comparing the clinical manifestations of COVID-19 and SARS, we see significant difference of cytokine storm between them. The clinical manifestations of SARS include high fever, cough, dyspnea, and fatigue. But the major symptom and significant feature of high fever of SARS suggest that its feature of cytokine storm is due to the increased activity of

inflammatory cytokines such as IL-1 and TNF-α. The fact that the major symptoms of COVID-19 are fatigue and relatively mild fever indicates that its feature is highly associated with increased activity of TGF-β.

Significance of clarifying the feature of Cytokine Storm

Clarifying the feature of cytokine storm of COVID-19 is helpful for selecting precise treatment and improving efficacy. Currently, there is antiviral agent, although something like Remdesvir might work, for COVID-19. Hydroxychloroquine (HCQ) has shown some effects when administered with azithromycin in some studies, but more recent study conclude that hydroxychloroquine alone is not effective for the treatment of COVID-19 and that the combination of hydroxychloroquine and azithromycin increases the risk of mortality [21-22]. Although the US FDA granted the emergency use of Remdesivir in April, 2020, and a recent report by Beigel et al concluded that Remdesivir was superior to placebo in shortening the time to recovery in patients who were hospitalized with Covid-19, Remdesivir does not seem to reduce COVID-19 mortality so far [23]. Thus, aside from symptomatic and supportive care, prevention and treatment of complications, various effective anti-TGF-β therapies should be explored, including cytokine therapy, cytokine neutralizing antibodies, glucocorticoids, Chinese herbs, drugs and substances that inhibit TGF-β activity and interfere with TGF-β signal transduction. Literature reports have supported that targeting TGF-β activity are effective against COVID-19. Some traditional Chinese drugs, such as *Suctellaria baicalensis* and *Utrica dioica* [24], as well as ginseng, have an inhibitory effect on TGF-β activity and can be used to alleviated symptoms of COVID-19[25]. Kaempferol, which can inhibit the secretion of mucus from goblet cells, is beneficial for the prevention and treatment of mucus hypersecretion of the lungs [26-27]. Diterpene phenol extract of *Rosmarinus officinalis* has been reported to inhibit TGF-β in rats [28]. N-acetylcysteine (NAC) was used for the prevention and treatment of Covid-19. NAC has mucolytic (anti-mucous) effects. In addition, NAC can inactivate TGF-β and prevent its

binding to its receptor [29]. Recently, we adopted a strategic approach to repurpose the use of clinically approved drugs against SARS-CoV-2. We uncovered that NAC is able to interrupt the spike protein of the virus and therefore, stop the virus from entering into the host cells. Our results support current clinical trials of NAC for treating severe COVID-19 patients [30].

Discussion

Medicine has made great progress in recognizing and detecting the substantial and structural changes of diseases. This is insufficient, however, to comprehensively understand and master the holistic dysfunctional changes of the whole body. The changing regulation and dysfunctional status of the cytokine network make it difficult to determine and identify only by detecting the content changes of a lot of or even all the cytokines. This study reveals the relationship between cytokines and clinical manifestations. The practical diagnostic model we used in identifying the features of cytokine storm could guide diagnosis and treatment of CODVID-19 and other infectious diseases.

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