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Short Commentary

Pulmonary Injury Mediated by Cytokine Storm during Viral Infection was ameliorated by Traditional Chinese Medicine

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Qing-Fei-Pai-Du Decoction, a Chinese herbal formula, has been found to improve acute viral respiratory injury mediated by cytokine storm. The mechanism by which it achieves this is by inhibiting the infiltration of neutrophils and inflammatory macrophages through the TAK1/IKK/NF-κB pathway.

Coronavirus Disease 2019 (COVID-19) caused by the infection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and yearly prevalent influenza has been a challenge to global public health due to their rapid spread and emergence of new variants. The cytokine storm, which is an immunopathological injury mechanism caused by the excessive activation of the immune system, is closely related to the pathological damage and mortality of viral infectious diseases, such as those caused by influenza virus and SARS-CoV-2 [1,2]. It is characterized by the high levels of cytokine secretion, including interleukins interleukin (IL)-6, IL-1β, Tumor Necrosis Factor (TNF)-α, Interferon-γ, and chemokine IL-8 [3]. In infectious diseases, these pro-inflammatory cytokines are induced by the over-activation of immune responses to infections – are key cytokines that are always over-expressed in cytokine storms and are thought to have crucial immunopathologic roles [4]. Patients with severe COVID-19 were found to exhibit higher levels of IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1, TNF-α, MIP-1α, and granulocyte-CSF compared to patients with mild and moderate infections(2). The severity of the cytokine storm is closely associated with the severity of adverse reactions, with more severe cases presenting with Acute Respiratory Distress Syndrome (ARDS), Multiple Organ Failure (MOF), and viral sepsis. Similar to COVID-19, multiple clinical studies have shown that the occurrence of a cytokine storm is associated with more severe tissue damage and poor prognosis for severe patients with influenza [4].

Both SARS-CoV-2 and influenza virus are single stranded RNA (ssRNA) viruses. Therefore, severe infections arising from these viruses have very similar pathological characteristics [5]. Toll-like receptor 7 (TLR7) and Retinoic Acid-Inducible Gene I (RIG-I) are major Pathogen Recognition Receptors (PRRs) that recognize viral nucleotides and activate the downstream signaling pathways to initiate antiviral immune response [6]. After ligation with ssRNA, TLR7 can recruit IL-1 Receptor-Associated Kinases (IRAKs) and Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF6) via the adaptor myeloid differentiation factor 88 (MyD88). Then, they activate the transforming growth factor Beta-Activated Kinase1 (TAK1)-IκB Kinase (IKK)- nuclear factor kappa B (NF-κB) cascade. The phosphorylated IKKα/β promotes the phosphorylation and degradation of the inhibitor of NF-κB (IκBα) [7] and the subsequent translocation of phosphorylated p65 into the nuclei, initiating the expression of a variety of cytokines and chemokines [8]. The chemokines Macrophage Inflammatory Protein-2 (MIP-2) and Monocyte Chemoattractant Protein-1 (MCP-1) then attract the chemotaxis and infiltration of neutrophils and monocytes/macrophages, contributing to the formation of cytokine storm and the subsequent tissue damages. These include diffuse alveolar damage, fibrin exudation, and even ultimately leading to multiple organ dysfunction [4] . TNF and IFN-γ are also known to cause cell death in multiple cell types, contributing to various pathological conditions such as Chronic Obstructive Pulmonary Disease (COPD), fibrosis, and osteoporosis, by activating inflammatory cell death, which presents with certain characteristics in murine macrophages, including: pyroptosis, apoptosis, and necroptosis [9].

The Qing-Fei-Pai-Du Decoction (QFPDD) is the recommended effective Chinese herbal formula in Version I to XI of the COVID-19 Diagnosis and Treatment Plan to treat patients in every clinical stage of COVID-19 infection. QFPPD can decrease the mortality rate of COVID-19 patients to 1.9% vs 4.8% in the control group [10], presenting with decreased levels of blood urea nitrogen, creatine kinase, lactate dehydrogenase, and C-reactive protein [11]. Aside from that, QFPDD can exert anti-inflammatory roles in dextran sulfate sodium (DSS)-induced colitis mice (12) and promote the recovery of lung inflammation as well as alleviate symptoms during the treatment of COVID-19 [12].

In the current issue of The American Journal of Chinese Medicine, Ye and colleagues provided new evidence of QFPDD in improving acute viral respiratory injury via inhibiting the cytokine storm in influenza virus-infected mouse model [13]. The study used an acute severe infective model, wherein C57BL/6 mice were infected by influenza

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virus A/Puerto Rico/08/1934 (PR8). The results showed that the oral administration of QFPDD ameliorated weight loss, increased survival rate, reduced lung indexes, ameliorated lung pathological damage, etc. Besides that, the expression of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) and chemokines (MCP-1) were down-regulated dramatically in lung tissues, broncho-alveolar lavage fluids (BALFs), and serum samples. Meanwhile, the anti-inflammatory cytokine IL-10 was increased in the lung tissues of flu mice, suggesting that QFPDD significantly reduced the excessive inflammatory response, inhibited the formation of cytokine storm, and subsequently offered protection for flu mice.

The proportions of neutrophils and macrophages in BALFs obtained from severe COVID-19 patients were higher than that those in moderate patients [14]. Ye, et al., also reported that neutrophils and macrophages are the most critical contributors to the cytokine storm identified in HCoV-229E-infected lungs of mice in a cold and damp environment, based on the single-cell RNA sequencing (scRNA-seq) analysis. However, QFPDD could decrease their proportions and inflammatory scores, significantly down-regulating various inflammatory cytokines overexpressed in neutrophils and macrophages, such as Nfkbia, Cxcl2, Cxcl1, Il1a, and Ccl3 in macrophages, as well as Nfkbia and Tnf in neutrophils. The decreased expression of MCP-1 in BALFs of influenza virus-infected mice might account for the decreased infiltration of neutrophils and macrophages induced by QFPDD. Similar with the results of scRNA-seq data in HCoV-infected models, PR8 infection can also increase the proportion of infiltrating neutrophils and inflammatory monocytes/macrophages in the lungs of mice. Similarly, QFPDD treatment can significantly downregulate their proportions in flu-infected mice. Thus, it is clear that QFPDD can inhibit the infiltration of neutrophils and inflammatory macrophages in the lungs by regulating the overexpression of MCP-1 and other inflammatory cytokines in both HCoV and influenza infected mice – this might be the potential mechanism for the inhibition of cytokine storm. Meanwhile, the percentage of $CD8^+$ T cells was decreased in HCoV-infected mice; in response to this, QFPDD can restore the levels of $CD8^+$ T cells and other cells in the lungs to improve the cell ecological environment and ameliorate lung tissue damage.

The clinical data show that a large number of macrophages are enriched in the BALFs of severe COVID-19 patients [14] – these macrophages play a decisive role in the severity of inflammatory response and, subsequently, the clinical outcome of the respiratory virus infection. Typically, macrophages are diverse and plastic: the classically activated macrophages (M1) are pro-inflammatory and produce pro-inflammatory cytokines IL-6, TNF-α, IL-1β, IL-12, and IFN-γ; meanwhile, the alternatively activated macrophages (M2) are anti-inflammatory and pro-healing, producing anti-inflammatory cytokines, such as IL-10 and transforming growth factor beta (TGF-β). The imbalanced polarization of these two sub-types of macrophages is significantly associated with organ damage and a poor prognosis caused by infection [15]. Thus, rebalancing the ratio of M1/M2 macrophages is a promising anti-inflammatory strategy to treat such diseases.

In regards to this, Ye et al., [13]. also provide some evidence of the inhibitive effect QFPDD exerts on M1 macrophage (iNOS, CD86, IL-6, TNF-α, IL-1β, and COX-2) polarization with the restoration of balance between M1 and M2 in PR8-infected mice. In vitro, QFPDD-containing sera can significantly inhibit the polarization of M1 induced by IFN-γ and LPS in human primary $CD14^+$ monocytes from PBMCs. This therefore leads to the downregulated expression of M1-related inflammatory cytokines, such as IL-12, TNF-α, IL-6, IL-1β and IFN-γ. At the same time, QFPDD also upregulated M2 macrophage markers CD206 and IL-10 as well as CD86 on M1-macrophages, which is a key co-stimulator of antigen presentation. This further confirms that QFPDD may protect the host from overwhelming inflammatory damage mediated by M1-type cytokines by reducing the high M1/M2 ratio while maintaining antigen-presenting capacity. Interestingly, the results were similar to those found in the further reanalysis of the scRNA-seq data annotated by macrophages based on corresponding markers, with a reduced M1 (Tnf^+) macrophage proportion and an increased M2 ($Arg1^+$) macrophage proportion after QFPDD treatment in HCoV - infected mice.

Ye et al., [13] also showed that QFPDD-containing sera can downregulate the virus-induced expressions of inflammatory cytokines in macrophages in vitro. It reduces the secretion of pro-inflammatory cytokines (IL-6 and TNF-α) and chemokines (MIP-2, MCP-1, and IP-10) in virus-stimulated RAW264.7 cells with PR8 or imiquimod (R837), but promotes the expression of anti-inflammatory cytokine IL-10. Similar anti-inflammatory activities of QFPDD were also confirmed in PR8- or R837-stimulated mouse primary peritoneal macrophages and bone marrow-derived DCs (BMDMs). R837 is a synthesized single-stranded RNA and commonly used as the ligand of TLR7 to mimic RNA from viruses to activate TLR7 on macrophages, dendritic cells (DCs), etc., [16]. QFPDD-containing sera was reported to reduce the secretion of inflammatory cytokines (IL-6, TNF-α), and chemokines (MCP-1) in BMDMs stimulated by PR8 or R837; thus weakening the inflammatory response induced by the pseudoviral particles of SARS-CoV-2 in the primary mouse peritoneal macrophages, decreasing the production of IL-6, TNF-α, and MCP-1 but upregulating the expression of IL-10. The pseudoviral particles of SARS-CoV-2 stimulated cells were also used to mimic the immune response induced by SARS-CoV-2 infection to further investigate the anti-inflammatory role of QFPDD in the SARS-CoV-2-provoked immune response. The results suggested that QFPDD may play a dual immunoregulatory role in the excessive immune response induced by virus infection in both macrophages and DCs.

Other than that, QFPDD might suppress the production of pro-inflammatory cytokines by inhibiting the activation of the NF-κB signaling pathway and promote anti-inflammatory cytokine by increasing the phosphorylation of GSK3β after being triggered by viral RNAs through TLR7 in macrophages. The scRNA-seq data have shown that the NF-κB signaling pathway, the basic pathway downstream of TLR7, is crucial for the anti-inflammatory role of QFPDD during corona-viral infection. QFPDD-containing sera was found to inhibit the phosphorylation of TAK1, IKKα/β, IκBα, p65, as well as the translocation of phosphorylated p65 to nuclei to reduce inflammation in R837 triggered RAW264.7 cells, which could downregulate the levels of cytokine storm associated cytokines and chemokines, such as IL-1, IL-6, IL-8, IFN, MIP-2 and MCP-1. Moreover, MCP-1 and MIP-2 might also be related to the infiltration of neutrophils and macrophages in the lungs. QFPDD also increases the phosphorylation of GSK3β to some extent, which is critical for IL-10 expression in the macrophages and DCs and might account for enhanced IL-10 expression.

Traditional Chinese Medicine (TCM) is widely used in China to prevent and treat clinical diseases and health problems, and it is currently believed that several Chinese herbal medicines contain a variety of bioactive ingredients with a wide range of anti-inflammatory

effects and are often used as a natural and potentially safer source for drug discovery. QFPDD has been demonstrated by Ye et al. and others to be effective against a variety of respiratory viral infections such as influenza viruses and has a variety of immunomodulatory effects such as inhibiting cytokine storms. In this study, they provided further evidence that QFPDD exhibits its potential benefits in treating acute viral respiratory injury by preventing the cytokine storm. More specifically, it helps to reduce inflammatory damage by inhibiting the infiltration of neutrophils and inflammatory M1 type macrophages as well as the pro-inflammatory activity of macrophages through the TAK1/IKK/NF-κB pathway (Figure 1). The study provided the major mechanism of QFPDD in treating respiratory viral infection caused by influenza viruses, HCoV-229E, and SARS-CoV-2. This lays a theoretical foundation for clinical treatment, guiding better application of QFPDD, as well as facilitating the identification of clinical indications or adapting patients through the evaluation of inflammatory cytokines or related genes.

Without unifying definition, the cytokine storm is generally considered a kind of life-threatening systemic inflammatory syndrome involving abnormally elevated circulating cytokines. It is caused by the hyperactivation of immune cells triggered by various pathogens, immunotherapies, cancers, autoimmune and monogenic disorders, involving a complicated and interrelated network of immune cells, signaling pathways, and cytokines. A diverse array of cytokines and chemokines involved in cytokine storm disorders have been discovered, including IL-1, -2, -6, -9, -10, -12, -17, -18, -33, IFN-γ, GM-CSF, VEGF, IL-8, MIG, IP-10, MCP-1, MIP-1α, MIP-1β, BLC, etc. [3]. The research of Ye and colleagues also provides a theoretical basis for expanding the application of QFPPD in the treatment of other infectious or noninfectious diseases with cytokine storm as the main pathological mechanism. It also set up the exploration in new directions and fields of clinical drug application. Especially for ssRNA virus infection such as SARS-CoV-2, which is prone to mutations, there are a variety of bioactive ingredients in the TCM formula, which can jointly exert immunomodulatory effects through different mechanisms, and can play host-oriented therapeutic effects, focusing on regulating host function rather than direct antiviral therapy, thereby highlighting the advantages of TCM in regulating immunity, which may also be a good treatment strategy for dealing with viral mutations.

In Ye's study, it was also found that the levels of some other cells were changed in the corona-virus infection through scRNA-seq, which were also related to the extent of cytokine storm and lung injury. Therefore, evaluation and research on other cells are also valuable for more systematic analyses and disclosure of the treatment mechanisms of QFPDD. In addition, the key cells involved – neutrophils and macrophages – can be conditionally knocked out or knocked down to further evaluate their roles in lung injury resulting from SARS-Cov-2 infection. They can also be used to evaluate the anti-inflammatory effects of QFPDD to identify its therapeutic targets. In addition, the clarified effect and mechanism of QFPDD combined with Oseltamivir need to be further studied.

Upon PR8 or HCoV infection, TLR7 on the infected epithelial cells or innate immune cells bind with viral RNA from SARS-CoV-2 or influenza virus and activate the receptor associated downstream signaling pathways and initiate an antiviral immune response. TLR7 will recruit IRAKs and TRAF6 by the adaptor MyD88, and then activate the TAK1 - NIK - IKK cascade. The phosphorylated IKKα/β promotes the phosphorylation and degradation of IκBα, and the subsequent translocation of phosphorylated p65 into the nuclei. Finally, it initiates the expressions of a variety of cytokines (IL-1, IL-6, IL-8, type-I IFN); chemokines, (MIP-2, MCP-1), and eventually promotes the polarization of M1 macrophages. As a result, increasing numbers of neutrophils, inflammatory macrophages, and other inflammatory cells are activated and migrate to the sites of infection in the lungs. These over-activated immune cells can then secrete more cytokines and chemokines, contributing to the cytokine storm and leading to lung injury. QFPDD can counter this by inhibiting the expression of cytokines and chemokines as well as the infiltration of neutrophils. macrophages, and other innate immune cells. It does so by inhibiting the critical signaling molecules of the TAK1- NIK-IKK pathway. QPFDD can also suppress M1 polarization of macrophages and decrease cytokine expression to alleviating lung injury. Thus, QFPDD is able to protect mice from the lethal infection of influenza virus.

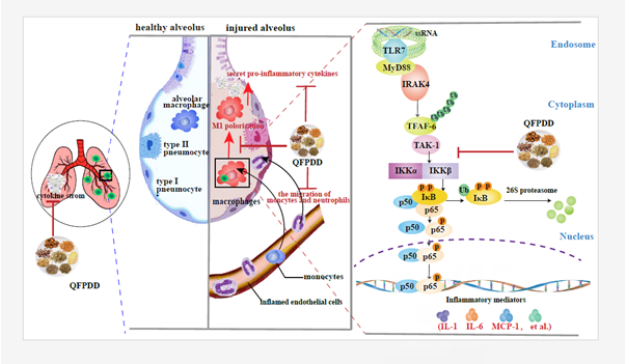

Figure 1: The immune protection mechanism and signaling pathway of QFPPD against cytokine storm-induced lung injury during viral infection.

*IRAKs: interleukin-1 (IL-1) receptor-associated kinases; TRAF6: tumor necrosis factor receptor-associated factor 6; MyD88: myeloid differentiation factor 88; TAK1: transforming growth factor beta activated kinase1; NIK: nuclear factor-kappa B (NF-κB)-inducing kinase; IKK: IκB kinase; IκBα: inhibitor of NF-κB; IFN: interferon; MIP-2: macrophage inflammatory protein-2; MCP-1: monocyte chemoattractant protein-1.

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