Commentary

A commentary of “Type I interferon deficiency can lead to severe COVID-19” in 10 remarkable discoveries from 2020 in Nature

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A B S T R A C T

In two articles published in Science online in September 2020, Zhang et al. [1] and Bastard et al. [2] elucidated a key factor in the progression to severe COVID-19; namely, a deficiency in interferon, especially type I interferon (IFN-I). This deficiency might be caused by diverse reasons such as genetic mutations of genes encoding key antiviral signaling molecules, or the ‘neutralization’ of IFN-I by endogenous antibodies. How does IFN-I deficiency cause severe, life-threatening COVID-19? The most straightforward explanation is that such deficiency allows uncontrolled virus replication and spread. IFN-I deficiency may also have other impacts on immune system function. Individuals with mutations in the IFN-I-induced signaling pathways may benefit from interferon therapies. In addition, individuals with neutralizing antibodies against IFN-α and IFN-ω may also benefit from other types of interferons provided in the therapy, such as IFN-β and IFN-λ.©

The COVID-19 pandemic caused by SARS-CoV-2 has caused more than 5 million deaths worldwide and has had an unprecedented impact on human society. The pandemic has severely endangered global health and has also pushed biomedical research to the frontline. Jean-Laurent Casanova et al. at the Rockefeller University in the US recently reported that IFN-I deficiency may worsen the process of COVID-19, with at least 10.2% of patients producing ‘inside man’ antibodies that attack the immune system itself instead of the virus. Moreover, 3.5% of patients with severe COVID-19 had mutations in IFN-1-related antiviral defense genes [3]. These findings revealed part of the mechanisms of COVID-19 pathogenesis and hinted at how it became life-threatening, which might change the vaccine distribution strategies of public health institutions and provide a new direction for COVID-19 treatment, making it indubitably one of the ‘10 remarkable discoveries from 2020’ by Nature.

Epidemiology studies have identified three risk factors for severe COVID-19 infections: male gender, older age, and underlying diseases. However, even taking these factors into account, large clinical differences still exist between individuals. Thus, how to reduce the mortality and improve the outcome of severe COVID-19 and how patients with COVID-19 can receive ‘customized’ therapy are unsolved. Exploring and elucidating the precise molecular mechanisms of COVID-19 infection and disease progression is fundamental for the prevention and treatment of severe COVID-19.

IFN-I (mainly including IFNα and IFN/β) is a key player among antiviral actions early during the infection. In 1957, Isaacs and Lindenman discovered IFN-I which demonstrated a natural and rapid antiviral activity. IFN-I works on the host cells as autocrine and paracrine factors to induce the expression of various IFN-stimulated genes (ISGs) to promote cellular antiviral activity. IFN-I is also a bridge linking the innate with adaptive immune systems [4]. When the virus infects the cells, IFN-I normally immediately induces strong local reactions to trigger the production of proteins by the infected cells to attack the virus, while also recruiting immune cells to the infection site and notifying adjacent cells to prepare for defense and battle [4]. Therefore, the normal functioning of IFN-1 directly affects COVID-19 progression. IFN-I deficiency may result in life-threatening viral infections. Why would the function of IFN-I fail during COVID-19 infections? How can we provide treatment targeting IFN-I malfunction? These are key issues in COVID-19 treatment.

Two studies published online in Science on September 24, 2020, elaborated on these issues and explained why COVID-19 is severe in certain populations. Bastard et al. analyzed blood samples from 987 patients with severe COVID-19 and found that 10.2% of the population had antibodies against IFN-I from the patient him/herself [2]. In addition, the blood interferon levels in these patients were extremely low or even undetectable. Further experiments confirmed that the autoantibodies disabled interferon and that cells exposed to IFN-I antibodies failed to combat SARS-CoV-2 infection. In contrast, none of the 663 patients with mild or asymptomatic SARS-CoV-2 infections, showed IFN-I autoantibodies. Zhang et al. performed DNA sequencing of 659 patients with severe COVID-19 along with 534 with a mild or asymptomatic disease as controls [1]. IFN-related genetic deficiency was identified in 3.5% of patients with life-threatening COVID-19. Cells that lacked IFN-related genes were more susceptible to SARS-CoV-2 infection.

These two studies provided key biomarkers and high-risk genetic markers for the early warning of severe COVID-19 infections. The detection of IFN-I-related genetic mutations, as well as IFN-I autoantibodies, can identify individuals at high risk for severe COVID-19, thereby allow-

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ing the implementation of key prevention and treatment measures. Exposure prevention and priority for vaccination are important during this stage. Secondly, IFN-1 autoantibodies may be produced during COVID-19 infection. Therefore, the timing of interferon administration is directly related to patient prognosis and the treatment should be administered as soon as possible. Thirdly, the inhibition of the autoantibodies in the IFN-1-mediated response may be a key mechanism for the deterioration of COVID-19. Plasma replacement to diminish autoantibodies may improve patient prognosis. Fourth, autoantibody detection must be performed when the plasma from the recovery period is used for treatment. The use of plasma-containing autoantibodies should be avoided. Lastly, recent studies have shown that patients with autoantibodies do not benefit from recombinant IFN-1 treatment. However, recombinant IFN-1 treatment can improve the prognosis of patients with IFN-1 but not IFNAR1 or IFNAR2 mutations. These findings have provided new ideas for precision medicine and individualized treatment of COVID-19.

Endogenous interferon deficiency plays a key role in the pathogenesis of COVID-19 infections. Multiple research teams in China have made a significant contribution to the prevention and treatment of COVID-19. Among these, academician Yunde Hou (recognized as the father of ‘interferon in China’) has developed a recombinant interferon α1b, the first genetic engineering drug in China. This upgraded interferon not only acted as a good antiviral agent but also did not induce excessive inflammation, which significantly reduced the side effects of interferon. Thus, this is an important candidate drug for the clinical treatment of COVID-19. The ‘recombinant human α-interferon’ developed by academician Wei Chen and her team during the severe acute respiratory syndrome (SARS) epidemic was approved for clinical use. The recombinant human α-interferon spray was used by medical staff to prevent SARS infection. In the field of traditional Chinese medicine, the combination of Qingfei Paidu decoction and the interferon-α was significantly effective in treating COVID-19, underscoring the increasing importance of traditional Chinese medicine in the prevention and treatment of major epidemics. The strong pass of the enemy is like a wall of iron, yet with firm strides, we are conquering its summit!

Declaration of Competing Interest

The author declares that she has no conflicts of interest in this work.

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Xiangming Fang received her M.D. from Bonn University in Germany, and finished her residency training and specialized in Anesthesia at Zhejiang University. Since 2003 she became a professor of Anesthesiology and Crit Care. Her research focuses on the non-toll receptor in sepsis and the management of perioperative sepsis. Based on her clinical trials, she drafted the consensus of management of perioperative sepsis.