Toward brighter tomorrow 35-217127, Ryo Nishiyama

Cytokine storm and COVID-19 treatment

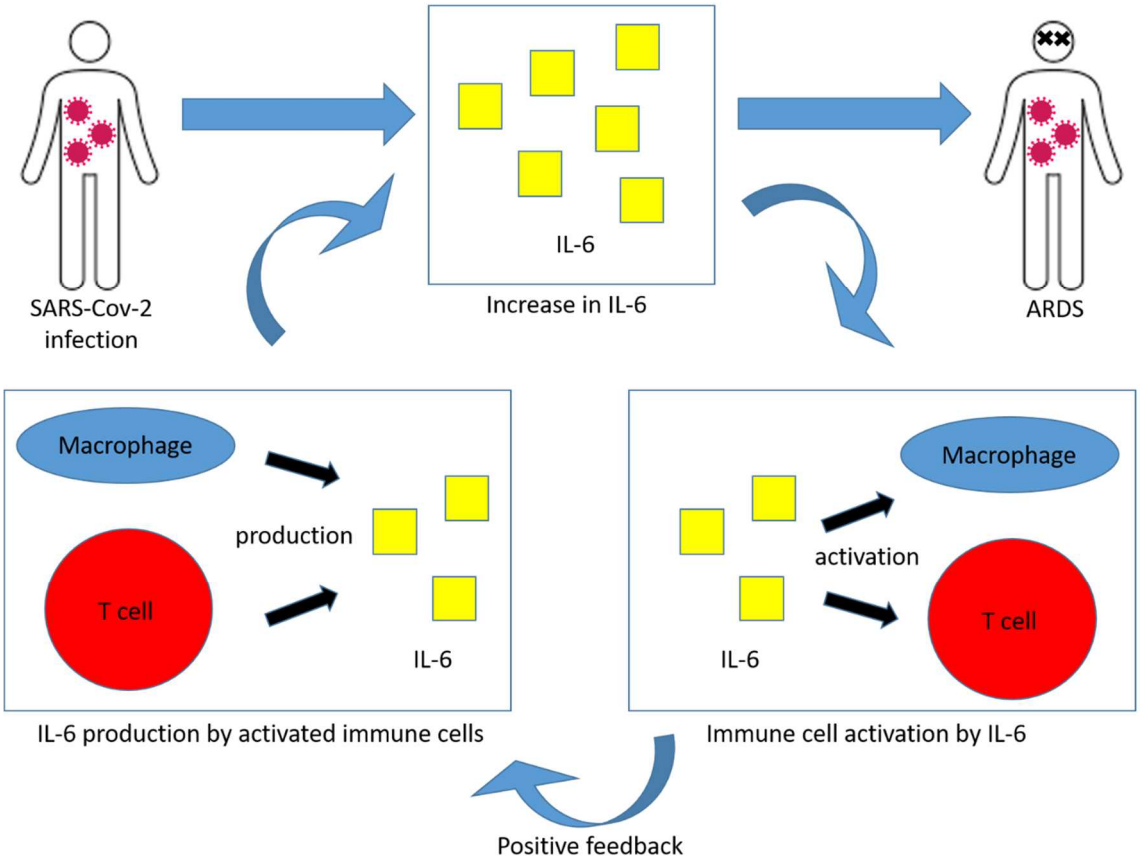

Fig.1: Mechanism of cytokine storm in COVID-19 patient

These days, SARS-CoV-2 outbreak has been one of the most serious problems in the world. To date, it is reported that more than 170 million people have been infected and more than 3 million people have died due to this new type of virus. This has also influenced our society seriously and changed our lifestyles. SARS-CoV-2 is not only characterized by its high contagiousness, but also known for the relatively high death rate (higher than that in seasonal influenza). It is known that most of COVID-19-related death

is caused by acute respiratory distress syndrome (ARDS)[1]. Therefore, understanding the mechanism of ARDS is important for diagnosis and treatment for severe COVID-19 patients. Unfortunately, there has been no silver bullet for COVID-19 treatment despite much effort of scientists and doctors. Therefore, it is important to establish the approach to treatment by understanding the mechanism of the disease.

Recently, scientists have revealed that some of ARDS is caused by cytokine storm[2], which is a kind of immunodysfunction where cytokines, a chemical used for the communication between immune cells, are overproduced. In the mechanism of cytokine storm, IL-6, a sort of cytokine, plays an important role[3]. The cytokines are produced in a large amount when the patients are infected with SARS-CoV-2. Then, they affect some immune cells such as macrophages and T-cells and activate a transcription factor, STAT3. When STAT3 is activated in the cells, IL-6 production in the cells is promoted. Here, positive feedback in IL-6 production is formed and it results in an overproduction in IL-6. When IL-6 overproduction occurs, immune cells are proliferated and activated too much and they finally hurt patient's own body, which sometimes leads patients to death. This means that, many of the death cases in COVID-19 patients are not due to the viruses it selves, but due to their own immune systems.

This finding can potentially be applied to distinguish potential severe patients by quantifying immune cell populations and their signaling status. In recent studies, scientists have revealed that immune cell populations in severe COVID-19 patients are different from those in healthy donors and moderate COVID-19 patients. Moreover, cellular signaling level can be quantified by measuring the number of activated cytokine receptors and cytokine concentrations. For example, as the reception of IL-6 occurs as a phosphorylation of a transcription factor STAT3, it can be monitored by using the

chemical which selectively attaches to phosphatized STAT3 and quantizing the chemical by some methods such as mass cytometry and flow cytometry. Also, there is an established way to quantify cytokine concentration and it can easily be executed by using some commercially available toolkits. If the distinction of potential severe COVID-19 patients can be realized by the combination of the methods illustrated above, COVID-19 treatments in the hospitals will be more effective than it is now. Also, there are some special treatments for the patients suffering from cytokine storm, which is explained in the following part in this essay. Therefore, it is expected that the diagnosis based on these methods will decrease the death rate in COVID-19 patients, especially those who are suffered from a cytokine storm.

Moreover, scientists have elucidated that inhibition to IL-6 signaling pathway could be a solution for this problem. This is the method which has originally been established for the treatment of rheumatism and it is confirmed to be valid. In the study of the treatment for rheumatism, Tocilizumab, an inhibitor to IL-6 acceptor, is widely used. Scientists have applied this chemical to COVID-19 patients and the validity of this method is confirmed in some studies[4], even though it is concluded to be invalid in some other studies. Also, some other study has reported Tocilizumab returns the immune cell populations to normal. At least, these results imply the potential of this method for COVID-19 treatment.

Furthermore, there are some more chemicals which can be used for cytokine storm treatment potentially, such as Sarilumab and Siltuximab. These drugs have also been used for the treatment of the diseases such as rheumatism. In fact, some studies have shown that Sarilumab-based treatment is also valid for severe COVID-19 patient[5]. As the properties of these drugs are all different, in terms of working mechanism and side effects, it is important to select the drug which is good for the patient. For this purpose, the

diagnosis method based on the quantifications of some parameters in immune cells illustrated above will also be beneficial. That is, monitoring immune status in the patient can help the doctors to select the best way of treatment specific to each patient.

In summary, I believe that the findings about cytokine storm mechanism can be beneficial for the treatment of COVID-19 patients, in terms of diagnosis and drug discovery. This will result in a drop in the death rate in COVID-19 patients and help the people all over the world to be live with a safe. It is expected that scientists proceed with this kind of research further and further and finally realize this goal.

References

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