Okayama University Medical Research Updates （OU-MRU） 2022.09 Vol.104

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Okayama University research: The determinants of persistent and severe COVID-19 revealed

(Okayama, 16 September) **In a study recently published in the journal *iScience*, researchers from Okayama University predict disruptions in the immune system that can lead to long-term or severe COVID-19.**

As COVID-19 wreaks havoc across the globe, one characteristic of the infection has not gone unnoticed. The disease is heterogeneous in nature with symptoms and severity of the condition spanning a wide range. The medical community now believes this is attributed to variations in the human hosts' biology and has little to do with the virus per se. Shedding some light on this conundrum are Associate Professor SUMI Tomonari from Okayama University, Research Institute for Interdisciplinary Science (RIIS) and Associate Professor Kouji Harada from Toyohashi University of Technology, the Center for IT-based Education (CITE). The duo recently reported their findings on imbalances in the host immune system that facilitate persistent or severe forms of the disease in some patients.

The researchers commenced their study by computer simulations with models based on a host's immune system and its natural response to SARS-CoV-2 exposure. Mathematical equations for the dynamics of cells infected by SARS-CoV-2 were plugged in to predict their behavior. Now, the immune system has messenger cells known as dendritic cells (DCs). These cells report information (in the form of antigens) about the invaders to the warriors, or T cells, of the immune system. The model showed that at the onset of infection, DCs from infected tissues were activated and then antibodies to neutralize SARS-CoV-2 gradually started building.

To investigate long-term COVID-19, the behavior of DCs 7 months after infection was evaluated by the computer simulation. the baseline model simulation revealed that DCs drastically decreased during the peak of infection and slowly built up again. However, they tended to remain below pre-infection levels. These observations were similar to those seen in clinical patient samples. It seemed like low DC levels were associated with tenacious long-term infection.

The subsequent step was to understand if DC function contributed to disease severity. It was found that a deficiency of the antigen-reporting function of DCs and lowered levels of chemicals known as interferons released by them were related to severe symptoms. A decrease in both these functions resulted in higher amounts of virus in the blood (viral load). What's more, the researchers also found two factors that affected the virus's ability to replicate in the host, namely, antigen-reporting DCs and the presence of antibodies against the virus. Anomalies in these functions could hamper viral clearance, enabling it to stay in the

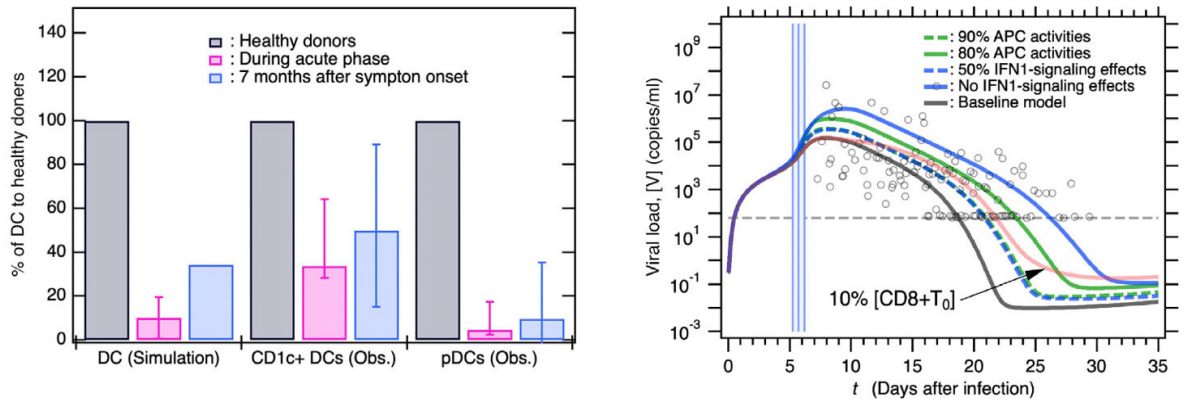
body longer than expected, whereas a high ability of these immune functions suppresses viral replication and yields prompt viral clearance.

Components of immune signalling that directly affect the outcome of COVID-19 infection were revealed in this study. " Our mathematical model predicted the persistent DC reduction and showed that certain patients with severe and even mild symptoms could not effectively eliminate the virus and could potentially develop long COVID," concludes the duo. A better understanding of these immune responses could help shape the prognosis of and therapeutic interventions against COVID-19.

Background

Dendritic cells and the immune system: Dendritic cells (DCs) are part of the body's innate immune system and are present in areas that come in close contact with pathogens such as the skin, respiratory tract, and gastrointestinal tract. When these tissues are infected, the DCs collate information about the pathogen and display it. DCs are now activated and transform into antigen-presenting cells (APCs). APCs then migrate to the lymph nodes where T cells reside to report this information. The T cells then migrate to and kill the invading pathogens. DCs also play a role in inflammation, a protective mechanism of the body, by releasing interferons. Interferons are chemical messengers that warn neighboring cells of a viral infection.

It is known that although the numbers of DCs do not change with age, their function is impaired. Since older patients have a higher proclivity for developing severe COVID-19, the patterns of DC function in severe infection were thus investigated by the computer simulation experiments.



Figure

Left. Proportion of DCs in healthy individuals, during acute COVID-19 infection, and 7 months after infection based on simulations and clinical observations (Obs).

Right. Comparison of viral loads between the baseline model and the severe symptom models with varying conditions of antigen-reporting DC function (APC) or interferon levels.

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Reference
Tomonari Sumi, Kouji Harada. Immune response to SARS-CoV-2 in severe disease and long COVID-19. *iScience*, 25, 104723.
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Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html

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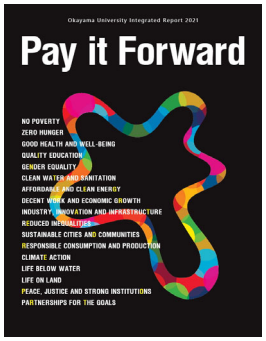

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