RESEARCH NEWS STORY

Could Auto-antibodies Be Linked to Severe COVID-19?

Researchers reveal auto-antibodies to type I IFNs block IFN signaling, contributing to severe COVID-19 by impairing the immune response

Recently, scientists found that some people who suffered from COVID-19 had auto-antibodies targeting their own type 1 interferons, which are important immune signaling proteins. Now, researchers conducted an in-depth study on 123 Japanese COVID-19 patients to clarify just how common these auto-antibodies are among severe cases and how they affect the immune system. Their findings could shed light on the role of auto-antibodies in exacerbating COVID-19 severity.
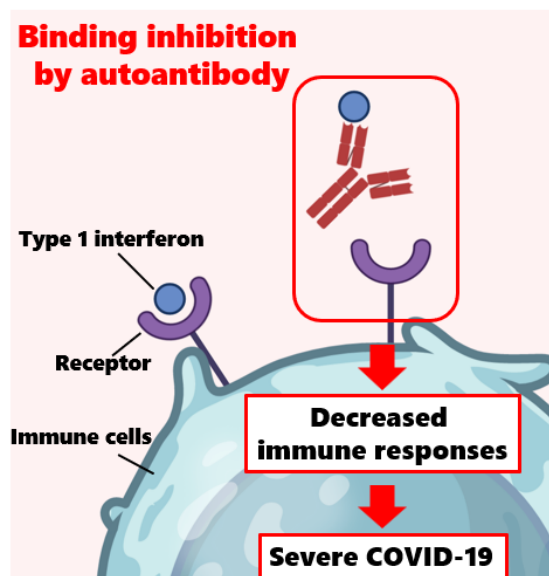

Image title: Auto-antibodies can neutralize type 1 interferons and compromise the immune response
Image caption: Auto-antibodies erroneously target their own proteins and enzymes. When these auto-antibodies target type 1 interferons, they can neutralize their function as signal proteins for the immune system. This study showed that some severe cases of COVID-19 were associated with the presence of auto-antibodies to type 1 interferons, shedding light on why some COVID-19 infections are severe without any other obvious risk factors.
Image credit: Chiaki Iwamura from Chiba University
Image license: Original content
Usage restrictions: Cannot be reused without permission

Even though COVID-19 manifests as a mild and short-lived disease in most people, some suffer extremely severe symptoms; in the worst cases, these patients die due to complications such as respiratory failure or thromboembolism. It is well-known that factors such as age and underlying medical conditions like diabetes or immunodeficiencies increase vulnerability to severe COVID-19. However, some patients still experience severe COVID-19 without any apparent reason.

One possible explanation may lie in auto-antibodies, which are antibodies that erroneously target specific proteins produced by one's own body. In normal circumstances, type I interferons (or 't1-IFNs') play a crucial role in the body's defense against viral infections; they interfere with viral replication and help mobilize the immune system. However, auto-antibodies against t1-IFNs can neutralize their activity, compromising the body's defense mechanisms. While detecting these auto-antibodies was uncommon before COVID-19, there have been multiple reports of severe COVID-19 patients bearing them since the pandemic started. Could auto-antibodies targeting t1-IFNs be more common than previously thought?

To answer this question, a research team, including Lecturer Chiaki Iwamura from Chiba University, Japan, investigated whether and how auto-antibodies targeting t1-IFNs are related to COVID-19 severity by analyzing blood samples from 123 Japanese patients. Their findings were published in Volume 44 of the *Journal of Clinical Immunology* on April 22, 2024. This research was co-authored by Dr. Kiyoshi Hirahara and Dr. Koutaro Yokote from Chiba University, as well as Dr. Ami Aoki from Niigata University.

The researchers first conducted an enzyme immunoassay to detect auto-antibodies to t1-IFNs in the blood samples, and then confirmed whether these antibodies could effectively neutralize t1-IFNs in cell cultures. "*We found that three out of 19 severe and four out of 42 critical COVID-19 patients had neutralizing auto-antibodies to t1-IFNs. Interestingly, there were no characteristic clinical features among patients with auto-antibodies to t1-IFNs,*" comments Dr. Iwamura. In other words, there were no pointers in the data as to why some COVID-19 patients developed these auto-antibodies, even when considering previous infections, treatments received, and underlying immune disorders. "*Based on these findings, it is difficult to estimate the presence of auto-antibodies to t1-IFNs from the usual blood tests and clinical background,*" remarks Dr. Iwamura.

To shed some light on how auto-antibodies to t1-IFNs affected COVID-19 patients, the researchers then conducted RNA sequencing and B cell receptor analyses. These experiments showed that conventional dendritic cells and canonical monocytes, two types of white blood cells, exhibited attenuated IFN signaling for patients in which auto-antibodies were present. Moreover, B cells (yet another type of immune cell) in these patients had fewer SARS-CoV-2-specific receptors, implying reduced effectiveness in combating an infection.

Overall, these findings highlight the importance of looking at auto-antibodies to t1-IFNs in more detail when facing viral epidemics. "*People with auto-antibodies to t1-IFNs are more susceptible not only to SARS-CoV-2 but also to common viruses such as influenza and to unknown viruses that may emerge in the future,*" warns Dr. Iwamura, "*Thus, we hope to*

collaborate with companies to develop a system to detect auto-antibodies to t1-IFNs in the blood. Ideally, we would develop a test to examine the presence of these auto-antibodies in regular health checkups so that people will be able to know whether they have them with little burden."

Let us hope their vision becomes a reality soon so that we can be better prepared to diagnose, prevent, and fight viral infections.

About Lecturer Chiaki Iwamura
Dr. Chiaki Iwamura obtained a PhD from Chiba University in 2008, where he served as Assistant Professor from 2008 to 2012. He was a Fellow of the National Institutes of Health, and is currently a Senior Lecturer at Chiba University. His research focuses on immunology, infectious disease, and allergies. He has published over 45 scientific papers in these fields. He is also a member of the Japan Society for Immunology.

Reference:
Title of original paper: Suppression of Type I Interferon Signaling in Myeloid Cells by Autoantibodies in Severe COVID-19 Patients
Authors: Ami Aoki[1,2], Chiaki Iwamura[1,3], Masahiro Kiuchi[1], Kaori Tsuji[1], Atsushi Sasaki[1], Takahisa Hishiya[1], Rui Hirasawa[1], Kota Kokubo[1], Sachiko Kuriyama[1], Atsushi Onodera[1], Tadanaga Shimada[4], Tetsutaro Nagaoka[5], Satoru Ishikawa[6], Akira Kojima[6], Haruki Mito[7], Ryota Hase[7], Yasunori Kasahara[8], Naohide Kuriyama[9], Sukeyuki Nakamura[10], Takashi Urushibara[11], Satoru Kaneda[12], Seiichiro Sakao[13], Osamu Nishida[9], Kazuhisa Takahashi[5], Motoko Y. Kimura[3,14], Shinichiro Motohashi[15], Hidetoshi Igari[16,17], Yuzuru Ikehara[18], Hiroshi Nakajima[3,17,19], Takuji Suzuki[3,20], Hideki Hanaoka[3,21], Taka-aki Nakada[4], Toshiaki Kikuchi[2], Toshinori Nakayama[1,22], Koutaro Yokote[23], and Kiyoshi Hirahara[1,3,22]
Affiliations:
1. Department of Immunology, Graduate School of Medicine, Chiba University
2. Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences

3. Synergy Institute for Futuristic Mucosal Vaccine Research and Development, Chiba University
4. Department of Emergency and Critical Care Medicine, Graduate School of Medicine, Chiba University
5. Department of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine
6. Funabashi Central Hospital
7. Department of Infectious Diseases, Japanese Red Cross Narita Hospital
8. Department of Respiratory Medicine, Eastern Chiba Medical Center
9. Department of Anesthesiology and Critical Care Medicine, School of Medicine, Fujita Health University
10. Funabashi Municipal Medical Center
11. Kimitsu Chuo Hospital
12. Department of Gastroenterology, NHO Chiba Medical Center
13. Department of Pulmonary Medicine, International University of Health and Welfare Narita Hospital
14. Department of Experimental Immunology, Graduate School of Medicine, Chiba University
15. Department of Medical Immunology, Graduate School of Medicine, Chiba University
16. Department of Infectious Diseases, Chiba University Hospital
17. COVID-19 Vaccine Center, Chiba University Hospital
18. Department of Pathology, Graduate School of Medicine, Chiba University
19. Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University
20. Department of Respirology, Graduate School of Medicine, Chiba University
21. Clinical Research Center, Chiba University Hospital
22. AMED-CREST, AMED
23. Department of Endocrinology, Hematology and Gerontology, Graduate School of Medicine, Chiba University

Contact: Chiaki Iwamura
Graduate School of Medicine, Chiba University
Email: iwamurac@chiba-u.jp

Public Relations Office, Chiba University
Address: 1-33 Yayoi, Inage, Chiba 263-8522 JAPAN
Email: koho-press@chiba-u.jp
Tel: +81-43-290-2018