COVID-19

https://doi.org/10.1038/s41590-023-01455-8

The kinetics of chemokine autoantibodies in COVID-19

Furong Qi, Dapeng Li & Zheng Zhang

Several panels of naturally arising antibodies against specific chemokines are closely correlated with various favorable COVID-19 outcomes, raising an opportunity to target the chemokine system for long COVID treatment.

Chemokines are a large family of small cell signaling proteins, which, in conjunction with their cell surface G protein-coupled heptahelical chemokine receptors, are essential for virus control through the recruitment of immune cell subsets to the infection site. Chemokines are directly involved in the acute phase of SARS-CoV-2 infection[1,2]. Naturally arising antibodies against cytokines and immune-effector molecules have been described to be associated with adverse outcomes in COVID-19 (ref. [3]). In the current issue of *Nature Immunology*, Muri et al.[4] characterize the kinetics of 43 chemokine autoantibodies at the acute and convalescence phases of COVID-19 (ref. [4]), and report that chemokine-directed antibodies may be protective against collateral inflammatory damage in COVID-19.

Muri et al.[4] designed a peptide-based strategy to measure the antibodies against the N-loop of the 43 human chemokines. The authors first identified a 'COVID-19 signature' (autoantibodies to CXCL17, CCL19 and CCL22; Fig. 1) in a cohort of 71 people followed for 6 months after SARS-CoV-2 infection and 23 uninfected participants as control (the Lugano cohort). More than half (23/43) of the chemokine autoantibodies in post-SARS-CoV-2-infected people were significantly different from those of healthy controls. This 'COVID-19 signature' achieved a high accuracy in distinguishing post-SARS-CoV-2-infected individuals at 6 months after disease onset from healthy controls (96.8%), which was validated in two additional cohorts — the Milan cohort (89.5% accuracy at 7 months) and the Zurich cohort (92.9% accuracy at 13 months). In addition, the 'COVID-19 signature' assigned individuals to acute COVID-19 or healthy control groups with an accuracy of 90.5% in the Milan cohort. CXCL17 is generally produced by macrophages, dendritic cells and monocytes in the lungs, and potentially promotes the mobilization of cytotoxic T cells through the CXCL17–CXCR8 axis. CCL22 is mainly secreted by dendritic cells and macrophages and modulates regulatory T cell migration through CCL22–CCR4 signaling. CCL19 is mainly expressed on dendritic cells and has a vital role in the

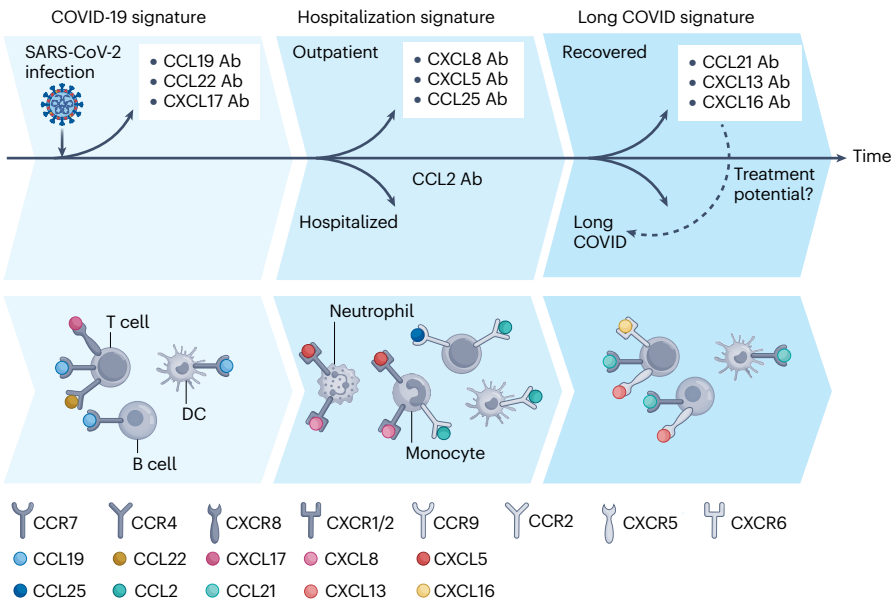

Fig. 1 | Distinct chemokine autoantibodies correlate with SARS-CoV-2 infection, favorable disease outcomes and lack of long COVID. Muri et al.[4] show that chemokine autoantibodies are widespread after SARS-CoV-2 infection. The 'COVID-19 signature' (autoantibodies to CXCL17, CCL19 and CCL22; left panel) is elevated in SARS-CoV-2-infected individuals compared with that in uninfected controls, and might block the migration of T cells, B cells and dendritic cells (DCs) into the tissue. The 'hospitalization signature' (autoantibodies to CXCL5, CXCL8 and CCL25; middle panel) is found in outpatients, and might block the migration of neutrophils, monocytes, DCs and T cells into the tissue. The 'long COVID signature' (autoantibodies to CXCL13, CXCL16 and CCL21; right panel) is higher in people without long COVID, and might block the migration of T cells, B cells and DCs into the tissue.

trafficking of T cells and B cells to the secondary lymphoid organs. As such, the COVID-19 signature-related chemokines are important effector molecules in priming the innate and adaptive immune responses to exert anti-viral functions during the acute phase of COVID-19.

Muri et al.[4] also performed a stratified analysis according to the disease severity of acute COVID-19. They found that the chemokine autoantibody signatures that distinguish post-COVID-19-infected individuals from healthy controls are significantly different from those associated with disease severity. A 'hospitalization signature' (autoantibodies to CXCL5, CXCL8 and CCL25; Fig. 1) was higher in outpatients than in individuals who required hospitalization. This signature can correctly distinguish hospitalized and outpatient individuals at 6 months with an accuracy of 77.5%. Similar accuracies were observed in the acute phase in the Milan cohort (85.0%), at 7 months in the Milan cohort (84.1%) and at 13 months in the Zurich cohort (73.1%). In addition to these three chemokine autoantibodies, outpatients had a significantly higher magnitude of cumulative chemokine autoreactivity than that in hospitalized individuals at 6 months post-COVID-19. CXCL5 and CXCL8 mainly recruit immune-suppressive myeloid cells to the site of infection through their receptors CXCR1 and CXCR2 (ref. [5]). CCL25 is believed to regulate inflammatory processes such as T cell homing and chronic tissue inflammation by binding to CCR9. To some extent, the increased amount of autoantibodies to CXCL5, CXCL8 and CCL25 indicated that the blockade of these chemokines during SARS-CoV-2 infection may repress excessive inflammation and protect the lung.

Importantly, Muri et al.[4] also identified a 'long COVID signature' (Fig. 1). Of all participants, 65.1% reported the persistence of at least one symptom related to COVID-19. The syndrome is often referred to as post-acute sequelae of SARS-CoV-2 infection, long COVID or post-COVID-19 condition[6]. The underlying biological mechanisms of long COVID are still poorly understood, possibly linked to immune dysregulation, autoimmunity and viral persistence[6]. Muri et al.[4] reported that autoantibodies to three chemokine (CXCL13, CXCL16 and CCL21), which constituted the 'long COVID signature', were significantly accumulated in post-COVID-19-infected individuals without long COVID (Fig. 1). The presence of these autoantibodies potentially predicted the absence of persistent symptoms with 77.8% accuracy, which indicates a protective role against collateral inflammatory damage during COVID-19. Validation of the 'long COVID signature' was also performed in the Zurich cohort with an accuracy of 72.1%. Although it is unclear how these chemokine autoantibodies contribute to recovery without long COVID, functional roles for these chemokines have been reported. CCL21, CXCL13 and CXCL16 mediate the transport and activation of T and B lymphocytes between the tissue and the peripheral blood. Large numbers of virus-specific T cells were reported to be associated with increased systemic inflammation and decreased pulmonary function in patients with long COVID[7]. SARS-CoV-2-specific memory B cells were also found to be increased in the bronchoalveolar lavage fluid of individuals post-COVID-19 infection compared with those in non-infected healthy controls[8]. Muri et al.[4] further validated that the monoclonal antibodies binding to the N-loop of CXCL13, CXCL16, CCL8 and CCL20 from a subset of post-COVID-19-infected individuals could inhibit immune cell migration. These studies thus suggest that blocking the chemokines that are involved in lymphocyte-sustaining activation might be a therapeutic target against long COVID through antagonizing specific chemokines on their N-loop.

Muri et al.[4] also tested if chemokine autoantibodies can be detected in people with HIV, three autoimmune diseases (ankylosing spondylitis, rheumatoid arthritis and Sjögren syndrome) and Lyme disease. The disease-specific patterns of chemokine autoantibodies could distinguish COVID-19 from other infections and autoimmune diseases. For instance, HIV-1 infection did not induce a significant increase in autoantibodies to CXCL17 or CCL19 (the 'COVID-19 signature'). The presence of the disease-specific chemokine autoantibody patterns highlights its unique role in the pathogenesis and the therapy of various diseases. Future studies are needed to investigate whether such kinetics of chemokine autoantibody profiles are also observed in other viral infections.

Consistently, the levels of several chemokines have been demonstrated to be abnormally elevated in COVID-19 and to be associated with poor outcomes, including respiratory failure, intensive care unit, mortality and long-term persistent impairment[3,6]. Muri et al.[4] found that the presence of various chemokine autoantibody signatures is associated with disease-specific responses, better disease outcomes of COVID-19 and the lack of long COVID (Fig. 1). These findings indicated that chemokine autoantibodies are potentially protective in a subset of patients with COVID-19, for they inhibit immune cell migration. This provides new insights for future COVID-19 studies about chemokine autoantibodies, especially in risk prediction, immune pathogenesis and targeted therapies.

First, it will be of importance to validate the presence of chemokine autoantibody patterns in a larger population, although the authors have validated their observation in two additional cohorts. Longitudinal follow-up of cohorts should be conducted to explore whether the elevation of chemokine autoantibodies that are associated with the absence of long COVID are already present in the acute phase or the early recovery stages and to further study their predictive value. In addition, it is not clear whether various patterns of chemokine autoantibodies can be defined in patients with long COVID with different organ-specific symptoms (for example, respiratory symptoms versus neurological symptoms), given the heterogeneity of symptoms, and even in long-term sequelae caused by other viral infections.

Second, it remains to be determined what drives the elevation of these autoantibodies in patients with favorable outcomes. A simple model would be that chemokines proportionally induce autoantibodies, but such a correlation was not found by Muri et al[4]. This may be partly owing to different sampling times and the variable half-lives for the chemokines and the autoantibodies in plasma. It will be important to determine whether the level of chemokine autoantibodies in the blood correlates with the amount of chemokines in the tissues. In autoimmune diseases, chemokines at autoimmune sites could cause the breakthrough of B cell tolerance to generate autoantibodies against the dominant chemokine at these sites[9]. A subset of patients with COVID-19 and individuals with long COVID can present inflammation- and autoimmune-related symptoms[10]. However, the chemokine autoantibody signature in COVID-19 is different from that in the autoimmune diseases that authors have investigated here. Future studies should elaborately investigate the mechanisms underlying the elevated chemokine autoantibodies in individuals post-COVID-19 infection without long COVID.

Third, given that the chemokine autoantibodies associated with long COVID are involved in sustaining lymphocyte recruitment, understanding the kinetics of these lymphocytes could help to clarify the mechanisms underlying the various COVID-19 outcomes. Research in the dynamics of antibody-producing cells and T cells through

single-cell transcriptomic analysis might lead to better understanding of these complex regulatory mechanisms[8]. Considering that naturally arising chemokine autoantibodies associated with COVID-19 may be beneficial in regulating inflammatory responses, the development of targeted therapies to the chemokine system will be critical in the treatment of long COVID.

Furong Qi[1,2], Dapeng Li[1,2] & Zheng Zhang[1]
[1]Institute for Hepatology, National Clinical Research Center for Infectious Disease, School of Medicine, The Second Affiliated Hospital Southern University of Science and Technology, Shenzhen, Guangdong Province, China. [2]These authors contributed equally: Furong Qi, Dapeng Li.
e-mail: zhangzheng1975@aliyun.com

Published online: 15 March 2023

References

1. Coperchini, F. et al. *Cytokine Growth Factor Rev.* **53**, 25–32 (2020).
2. Alon, R. et al. *Nat. Rev. Immunol.* **21**, 49–64 (2021).
3. Wang, E. Y. et al. *Nature* **595**, 283–288 (2021).
4. Muri, J. et al. *Nat. Immunol.* https://doi.org/10.1038/s41590-023-01445-w (2023).
5. Qin, G. et al. *Signal Transduct. Target. Ther.* **6**, 372 (2021).
6. Mehandru, S. et al. *Nat. Immunol.* **23**, 194–202 (2022).
7. Littlefield, K. M. et al. *PLoS Pathog* **18**, e1010359 (2022).
8. Cheon, I. S. et al. *Sci. Immunol.* **6**, eabk1741 (2021).
9. Karin, N. *Front Immunol.* **9**, 623 (2018).
10. Son, K. et al. *Eur. Respir. J.* **61**, 2200970 (2023).

Acknowledgements

Support was received from the National Science Fund for Distinguished Young Scholars (82025022), the R&D Program of Guangzhou Laboratory (SRPG22-006), the Shenzhen Science and Technology Innovation Committee (KQTD20200909113758004), the Central Charity Fund of Chinese Academy of Medical Science (2020-PT310-009), and the Emergency Grants for Prevention and Control of SARS-CoV-2 of Guangdong Province (2022A1111090001).

Competing interests

The authors declare no competing interests.