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EDITORIAL

Sensitive detection of anti-spike antibodies enables improved understanding of SARS-CoV-2 pathogenesis

Summary

Mass vaccination of the global population against SARS-CoV-2 will, we hope, turn the tide against this devastating pandemic. To complement vaccinations, better tools are needed to enable viral infections and immunological protection to be monitored. Accurate tools provide sound data for informed decision-making at many levels, from personal to governmental. The measurement of viral RNA is currently routinely used to detect active infections, but only gives a positive result during infection and is unable to reveal historic infections. Tests involving a detection of SARS-CoV-2-specific antibodies can reveal prior exposures to virus and can measure anti-viral immune responses induced after natural infection or after vaccination. They may eventually also be used to predict an individual's likelihood of becoming re-infected. Here, we report on the development of a sensitive ELISA technique to detect multiple isotypes of antibodies against the spike glycoprotein, in samples of both serum and saliva. This paper provides an important step towards understanding the immune response to SARS-CoV-2 and may therefore eventually help us to effectively control it.

The scientific community has made rapid advances in understanding the biology of SARS-CoV-2. These include the development of multiple effective vaccines [1] that are now beginning to ameliorate the effects of infections worldwide, and in identifying and testing strategies for the treatment of those unfortunate enough to be hospitalized after becoming infected. Parallel to these advances have been developments in our ability to detect both active viral infections and the potentially protective immune responses generated after an individual has been infected or vaccinated. The gold standard for detecting active infections is the PCR test. However, because PCR requires expensive specialist equipment, it is generally performed in centralized laboratories, with a consequent turnaround time in the order of 24 h. Thus, there is also a need for more rapid tests that can cheaply be performed at home. In the UK, this need for rapid detection of viral antigens is met by the use of lateral flow devices [2] designed to detect the expression of viral antigens.

While PCRs and antigen detection tests are important for detecting active infections, they are not able to reveal whether an individual has previously been exposed to the virus, or any of the characteristics of the immune response that is subsequently generated. These data are important for the assessment of, for instance, the level of protection against re-infection. This information about previous infections and the immune response can be generated in several ways, including the assessment of virus-specific T cells [3], or by measuring the SARS-CoV-2-specific antibodies produced by individuals after infection or vaccination. Antibody tests are highly specific and can be designed to identify responses to vaccine antigens, or to non-vaccine antigens. They can also be used to identify the immunoglobulin isotype of the detected antibody, giving additional information about the nature of the elicited immune response. However, the development of accurate assays is difficult and is affected by many factors, including an individual's level of infection, the site from which the sample is taken, and the detailed characteristics of the test that is used.

Analyses of SARS-CoV-2-specific antibodies have been developed and refined as the pandemic has progressed. The presence of higher levels of spike-specific IgA and IgG has been shown to correlate with increased severity of clinical disease [4]. More detailed analyses, the 'systems serology' approach [5], have revealed characteristics of antibody responses that differ between adults and children [6], and may therefore guide more sophisticated development of tailored vaccines in the future. In addition to antibodies specific for SARS-CoV-2 antigens, there is also interest in measuring auto-antibodies generated following infection. Tissue-specific autoantibodies can be detected after severe infections and may conceivably play a role in exacerbating viral-induced pathology [7].

For analyses of SARS-CoV-2-specific antibodies to be useful, there is a requirement for assays with high sensitivity and high specificity to detect the antibodies in available

biological samples. While antibodies are relatively easy to detect in people with severe disease, antibody tests are less reliable in people who are asymptomatic or who have mild symptoms. Here, we highlight a study from a team that has systematically developed a high-sensitivity ELISA, and used it to analyse the presence of anti-SARS-CoV-2 antibodies of IgA, IgG and IgM isotypes in both serum and saliva samples from non-hospitalized PCR-confirmed individuals [8]. The authors hypothesized that difficulties in detecting antibody positivity in individuals with milder infections may be caused by two factors: first, the available assays are relatively insensitive, and second, the mucosal and systemic immune responses are compartmentalized, so that antibodies circulating in serum may not readily be detected in the saliva samples that are more readily available for testing. Having systematically developed a highly refined ELISA using trimeric spike glycoprotein, they were able to detect immune response in people with low levels of infection. The most sensitive method for detecting infections required measurements of IgG, IgA and IgM to be combined. While the authors were able to detect anti-viral antibodies in saliva, saliva-positive individuals were less frequent than serum-positive individuals and tended to also display higher levels of anti-viral antibodies in their serum [8]. This work provides insight into the mechanisms controlling anti-viral antibody production in individuals with relatively low levels of infection. It therefore represents an important step in developing the tools necessary to understand the pathogenesis of SARS-CoV-2 infections, and make informed decisions about how best to prevent infections and treat disease.

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REFERENCES

1. Sharpe HR, Gilbride C, Allen E, Belij-Rammerstorfer S, Bissett C, Ewer K, et al. The early landscape of coronavirus disease 2019 vaccine development in the UK and rest of the world. Immunology. 2020;160:223–32.
2. Peto T, Affron D, Afrough B, Agasu A, Ainsworth M, Allanson A, et al. COVID-19: rapid antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation of sensitivity and specificity for mass-testing. EClinicalMedicine. 2021;30:100924.
3. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020;587:270–4.
4. Huang Z, Chen H, Xue M, Huang H, Zheng P, Luo W, et al. Characteristics and roles of severe acute respiratory syndrome coronavirus 2-specific antibodies in patients with different severities of coronavirus 19. Clin Exp Immunol. 2020;202:210–9.
5. Arnold KB, Chung AW. Prospects from systems serology research. Immunology. 2018;153:279–89.
6. Selva KJ, van de Sandt CE, Lemke MM, Lee CY, Shoffner SK, Chua BY, et al. Systems serology detects functionally distinct coronavirus antibody features in children and elderly. Nat Commun. 2021;12:1–4.
7. Richter AG, Shields AM, Karim A, Birch D, Faustini SE, Steadman L, et al. Establishing the prevalence of common tissue-specific autoantibodies following severe acute respiratory syndrome coronavirus 2 infection. Clin Exp Immunol. 2021;205:99–105.
8. Faustini SE, Jossi SE, Perez-Toledo M, Shields AM, Allen JD, Watanabe Y, et al. Development of a high-sensitivity ELISA detecting IgG, IgA and IgM antibodies to the SARS-CoV-2 spike glycoprotein in serum and saliva. Immunology. 2021;164:135–47.

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