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Commentary

Immunodominant epitopes based serological assay for detecting SARS-CoV-2 exposure: Promises and challenges

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The ongoing pandemic of COVID-19, caused by the novel coronavirus SARS-CoV-2, is a matter of global concern. As of late July 2020, the total number of confirmed COVID-19 cases worldwide has surged past 14 million, causing more than 600,000 deaths [1]. To impede its rapid spread, much of the world have resorted to partial or complete lockdown, resulting in an enormous social and economic impact. In the absence of any functioning vaccine or treatment, rapid and accurate detection of COVID-19 infections is crucial for limiting the associated disease burden.

Currently, reverse transcriptase real-time polymerase chain reaction (RT-PCR) based test of nasal and throat swabs is the gold standard for identifying COVID-19 infected patients. However, due to insufficient viral load at the time of testing [2], RT-PCR cannot detect previous exposure to SARS-CoV-2, which is important to evaluate the prevalence of infections in the population for devising measures to control virus transmission. In such cases, serological assays, which detect SARS-CoV-2-specific antibodies in blood samples of patients, could play a significant role by facilitating the identification of previous exposure to SARS-CoV-2. Serological assays can also assist in detecting a large number of subclinical infections in the community arising largely due to the high proportion of asymptomatic COVID-19 cases, and in identifying donors with highly reactive antibodies for convalescent plasma therapy. However, most of the SARS-CoV-2-specific serological assays reported so far in the literature employ recombinant proteins [3], which have several limitations. These include high storage constraints, batch-to-batch variations affecting reproducibility, and most importantly low sensitivity and specificity due to the presence of cross-reactive antibodies arising from previous exposure to genetically similar human coronaviruses [4] (seasonal coronaviruses as well as SARS-CoV, the causative agent of the 2003 SARS outbreak). Thus, there is an imminent need to develop improved serological assays for combating the ongoing COVID-19 pandemic.

In the current issue of *EBioMedicine*, Ng and colleagues attempt to address the above limitations of current serological assays by presenting a novel linear B cell immunodominant epitopes based assay for detecting exposure to SARS-CoV-2 [5]. Specifically, they identified a set of five immunodominant linear B cell epitopes from a peptide library of SARS-CoV-2 structural proteins by performing IgG reactivity test on pooled plasma samples of COVID-19 infected patients from Singapore. The identified epitopes were located on the spike and the nucleocapsid proteins of SARS-CoV-2. They then tested longitudinal IgG responses against these epitopes and found that four of the five identified epitopes could induce strong IgG responses in plasma of COVID-19 patients collected at different days (median 10 and 23 days) post infection. Importantly, no significant response was detected against these four epitopes in plasma samples collected from healthy donors and patients infected with seasonal human coronaviruses. Also, a very limited response was observed against these epitopes in recovered SARS individuals, despite the high sequence homology of these epitopes with corresponding regions in SARS-CoV [6]. Of the four identified epitopes, two epitopes individually reached sensitivity and specificity of $>$ 88% for detecting SARS-CoV-2 specific antibodies in plasma samples from COVID-19 patients at a median of 10 days post infection, while this percentage approached $>$ 90% at a median of 23 days post infection. Moreover, they demonstrated by statistical analysis that combining the two epitopes can approach the maximum sensitivity and specificity of 100%. Thus, an easy-to-use IgG lateral flow assay [4] designed based on the identified epitopes can potentially enable the development of a rapid and accurate point-of-care test (POCT) for SARS-CoV-2.

Consistent with multiple recent reports (e.g., [7,8]), the authors also found that the magnitude of IgG responses in COVID-19 patients against the identified epitopes correlated with disease severity. Further clinical studies are required to investigate whether the observed increase in IgG responses contributes to viral clearance. Remarkably, in contrast to antibody responses, SARS-CoV-2 T cell responses have been found to negatively correlate with disease severity in a preliminary study [7], suggesting the importance of T cells in preventing

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more severe COVID-19 symptoms. Taken together, these results are of paramount importance for the design of effective COVID-19 vaccines.

This work opens up multiple directions for future clinical research. For instance, while the proposed serological assay was tested on a small cohort of COVID-19 patients (n = 79), validation on a much larger cohort with different disease severity status (mild, moderate, and severe) will help to further strengthen its usefulness as a robust POCT. Moreover, as the prevalence of human coronaviruses differs globally, the performance of the proposed serological test in different geographical regions may greatly vary. Nevertheless, the impressive sensitivity and specificity achieved by the proposed assay in the Singapore population should motivate future clinical studies to investigate the utility of such serological assays in different populations.

Lastly, it is important to mention that recent SARS-CoV-2 preliminary clinical studies point to multiple potential limitations of serological assays. First, as antibody response in COVID-19 infected patients is known to be delayed (more than 7 days after onset of symptoms [9]), the serological assays may have very limited application in the identification of acute infections. Thus, serological assays cannot replace the current POCT based on RT-PCR, but instead, complement it for differentiating recent and previous exposure to SARS-CoV-2. Second, the usefulness of serological assays in detecting prior exposure relies on the stimulation and persistence of SARS-CoV-2-specific antibody responses in infected patients. There are recent preliminary studies that report the absence of seroconversion in mildly infected patients [10] and short duration of antibody-mediated immunity in asymptomatic patients [8], both of which can impede the performance of serological assays and result in underestimation of COVID-19 infections in the population. These also point to the perils of using COVID-19 “immunity passports” as antibody-mediated immunity may not confer protection from reinfection on subsequent exposure. While further clinical studies must be performed to confirm these characteristics of SARS-CoV-2 antibodies, testing for SARS-CoV-2-specific T cells, which have been reported to be relatively long-lived and detected even in the absence of seroconversion [10], may serve as an alternative to serological tests for assessing previous exposure to SARS-CoV-2.

Author contribution

AAQ drafted and approved the final manuscript.

Declaration of Interests

The author declares no conflict of interest.

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