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PERSPECTIVE

Comment on Tan *et al.*, page 746

Persistence of humoral and cellular immune response after SARS-CoV-2 infection: opportunities and challenges

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The emerging COVID-19 pandemic caused by SARS-CoV-2 infection has created a global crisis. Under the circumference of no effective treatment or vaccine, the Chinese government has implemented multifaceted measures of social distancing, home isolation, and centralized quarantine, which achieved a remarkable result of controlling the COVID-19 outbreak [1]. However, the personal, psychological, economic, and societal consequences of the shutdown and physical distancing make it difficult to sustain these public health interventions for a long time [2]. To find a new balance between curbing the pandemic and minimizing the indirect effects on society, a better understanding of adaptive immunity in response to SARS-CoV-2 infection is required. Monitoring B cell and T cell immunological memory activated by SARS-CoV-2 over a prolonged period is essential in anticipating durable protection after infection and in developing vaccines. If maintained at sufficiently high levels, the immune response could effectively block re-infection, which might confer long-lived protection [3,4]. Even though, the case report of re-infection with completely different SARS-CoV-2 strains from the first episode [5] raised widespread public concern for the "immune passport" and virus mutation. Despite the urgent need to answer these crucial scientific questions, limited studies have systemically evaluated the long-term humoral and cellular immunity.

Therefore, the study by Tan *et al*. [6] has great importance in filling the knowledge gap (Table 1 provides summaries of studies on the dynamics of antibody response after SARS-CoV-2 infection). The study reported that the IgG antibody of 17 COVID-19 patients were detectable at 6–7 months after diagnosis, although the concentrations were slightly lower compared to results in the early 2 weeks to 2 months. This is the longest observation of antibody dynamics to our best of knowledge so far. Another novel observation from this study was that 14 samples showed durable neutralizing activities in a pseudovirus assay, with no difference in blocking the cell-entry of the 614D and 614G variants of SARS-CoV-2 [6]. Moreover, the study [6] provided compelling evidence that both interferon γ-producing $CD4^+$ and $CD8^+$ T cells were increased in response to SARS-CoV-2 antigen stimulation as compared with non-stimulated samples at 6–7 months post-infection. Taken together, this study has provided the most updated evidence for the persistence of humoral and cellular immunity over a relatively longer period, and susceptibility to second infection for mutant coronavirus among convalescent patients. As the level of neutralizing antibodies against the SARS-CoV-2 spike protein (to block viral entry) is the key to evaluate the protection against re-infection, these findings would inform therapeutic strategies and guide public health intervention.

The study by Tan *et al*. [6] has its limitation of small sample size and not using the plasma samples from the same patients in different periods. A recent serological study in Iceland [7] evaluated the longitudinal changes in antibody levels among 487 recovered patients with two or more serum samples and found that the antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis by RNA test [7]. On the contrary, some reports [8–10] observed decay in IgG or neutralizing antibodies among the recovered patients during 2–3 months post-infection, particularly among the asymptomatic participants [9,10]. The potential interpretations for the disparity may include the inherent difference of humoral immune responses for asymptomatic and symptomatic infections [11] (time course and duration), and the relatively short observation period of antibody dynamics (typically less than 4 months) in prior investigations [8]. The majority of

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Table 1 Summary of studies on the dynamics of antibody response after SARS-CoV-2 infection

Author	Study type	Study participants	Time after symptom onset or after diagnosis	Antibody	Key findings
To *et al*. [18] March, 2020	Cohort study	*N* = 23 (13 mild cases, 10 severe cases) Hong Kong, China	Within 1 month	Anti-NP IgM (EIA) Anti-NP IgG (EIA) Anti-RBD IgG (EIA) Anti-RBD IgM (EIA)	An increase was noted in IgG or IgM antibody levels against NP or RBD at 10 days or later after symptom onset
Long *et al*. [9] April, 2020	Cohort study	*N* = 285 (246 non-severe cases, 39 severe cases) Chongqing, China	Within 3 weeks	IgM (MCLIA) IgG (MCLIA)	IgM and IgG increased during the first 3 weeks after symptom onset IgM decreased after 3 weeks
Wang *et al*. [17] June, 2020	Cohort study	*N* = 70 (66 non-severe cases, 4 severe cases) Beijing, China	Within 3 months	Antibody (ELISA) Neutralizing antibody (by a modified cytopathogenic assay)	Antibody (ELISA) levels and neutralizing antibodies peaked on day 31–40 since symptom onset, and then decreased slightly
Long *et al*. [15] June, 2020	Cohort study	*N* = 74 (37 asymptomatic cases, 37 symptomatic cases) Chongqing, China	Within 2–3 months	IgG (MCLIA) Neutralizing antibody (pseudovirus neutralization assay)	IgG and neutralizing antibodies decreased within 2–3 months after infection
Ibarrondo *et al*. [8] July, 2020	Cohort study	*N* = 34 (30 confirmed cases, 4 close contacts) USA	Within 4 months	IgG (ELISA)	IgG decreased rapidly during the observation period
Wu *et al*. [16] August, 2020	Cohort study	*N* = 175 (175 mild cases) Shanghai, China	Within 1 month	Neutralizing antibody (viral cytopathology neutralization assay)	Neutralizing antibodies were detected in patients from day 4 to 6 and reached peak levels from day 10 to 15 after disease onset
Gudbjartsson *et al*. [7] September, 2020	Cohort study	*N* = 487 (487 recovered patients with two or more serum samples) Iceland	Within 4 months	IgM anti-N (ELISA) IgG anti-N (ELISA) IgA anti-S1 (ELISA) IgG anti-S1 (ELISA) Pan-Ig anti-N (ECLIA) Pan-Ig anti–S1-RBD (ELISA)	Antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis
Tan *et al*. [6] September, 2020	Retrospective study	*N* = 64 (15 cases at 2 weeks to 1 month, 20 cases at 1–2 month, 17 cases at 6–8 months, 12 healthy donors) Shanghai, China	Within 6–7 months	S-protein IgG (ELISA) N-protein IgG (ELISA) Neutralizing antibody (pseudovirus neutralization assay) T cell response (the interferon-γ producing $CD4^+$ T cells and $CD8^+$ T cells)	IgG and neutralizing antibodies were detectable at 6–7 months after diagnosis No difference in blocking the cell-entry of the 614D and 614G variants of SARS-CoV-2 by neutralizing activities Interferon γ-producing $CD4^+$ and $CD8^+$ cells increased in response to SARS-CoV-2 antigen stimulation as compared with non-stimulated samples at 6–7 months

Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; MCLIA, magnetic chemiluminescence enzyme immunoassay; ECLIA, elecsys chemiluminescence assay.

the plasmablasts (B cells) are short-lived, which may contribute to the decay of antibody levels after the acute phase of infection [4]. Meanwhile, the effector $CD8^+$ T cell response exhibited a similar pattern as the B cell [3,4]. After the early decay phase, serological memory is maintained by a smaller number of longer-lived plasma cells that provide sustained immunity in the absence of antigen [3,4]. Therefore, samples collected during the early recovery phases may reflect a transient waning process [3]. By contrast, observations over a prolonged period would lead to more accurate modeling of the immune response [3]. The findings would ease the public apprehension regarding the decline of neutralizing antibody levels and the possibility of subsequent infection. However, it remains largely unclear how long the antibodies will persist at the needed protection threshold, and more studies are still needed.

The outbreak of COVID-19 in China during early 2020 was mainly caused by the 614D SARS-CoV-2 variant. However, the emerging 614G SARS-CoV-2 variant occurs more frequently among the recently infected individuals, which was reported to be more infectious than the original 614D variant *in vitro* and animal studies [12]. In Tan *et al*.'s study, although most convalescent patients were infected by the 614D variant, the neutralizing activities in blocking the cell-entry of the 614D and 614G variants at 6 months post-infection showed no significant differences [6]. The results indicated that vaccines developed for the 614D variant might also confer protection for the 614G variant. B cells and T cells both play an important role in the immune protection against SARS-CoV-2. The antibodies are generated by B cells, which would recognize and bind to the coronavirus and prevent cell entry. On the other hand, T cells mainly function as a target for killing the infected cells [13,14]. Most existing literature regarding immune protection against SARS-CoV-2 discussed the sustainability of antibody response [7,15–18], whereas less evidence were available for T cells durability [14,19]. Tan *et al*.'s study highlighted that interferon γ-producing T cells ($CD4^+$ and $CD8^+$ cells) were increased in response to SARS-CoV-2 antigen stimulation as compared to non-stimulated samples during 6–7 months post-infection [6]. The finding has important implications for ongoing vaccine development.

Elucidating the persistence of humoral and cellular immunity would provide us a powerful tool for modeling individual immune protection and developing vaccine distribution plans. However, many of the critical variables of the immune response (e.g., neutralizing potency for mutant coronavirus and minimally needed protection threshold) still remain largely unknown. Although the whole world is now waiting for the results from phase 3 vaccine trials, the study by Tan *et al*. [6] has its unique contribution to help understand the durability of the antibody levels from nature infection. More studies with larger samples size and repeated measures are urgently needed to validate the findings.

Compliance with ethics guidelines

Tangchun Wu declares that he has no conflict of interest. This manuscript does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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