Editorial

Is cellular immunity the future key for deciphering and monitoring COVID-19 vaccines efficacy?

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Introduction

Although there is now incontrovertible evidence that vaccination against coronavirus disease 2019 (COVID-19) is the most effective means for reducing the likelihood of developing severe illness and complications (1), doubts are emerging as to whether the administration of repeated boosters doses of "standard" COVID-19 vaccines may be the best solution (2). This is a vital consideration, given that some countries (e.g., US and Italy among others) have already authorized the administration of more than one vaccine boosters to fragile and older subjects (3). However, there is also ongoing debate as to whether it may be worthwhile to extend the second vaccine booster to the general population. Although the administration of additional doses of COVID-19 vaccine 3–6 months after receiving the first vaccine booster is seemingly effective to increase the serum levels of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies (4), the efficacy of these antibodies against new and highly mutated variants (such as those belonging to the Omicron lineages) remain questionable, for at least two important reasons.

Clinical accuracy of current anti-SARS-CoV-2 immunoassays

The first important consideration is that the current generation of anti-SARS-CoV-2 immunoassays, either laboratory-based or manual (i.e., rapid, point-of-care or "portable"), have been constructed using recombinant antigens derived from the original sequence of the prototype virus. Therefore, although the results of these measurements will provide a reliable reflection of the total "family" of anti-SARS-CoV-2 circulating antibodies elicited by vaccination or infection by ancestral variants, a great part of these immunoglobulins may no longer be effective to bind (and thus neutralize) new and highly mutated lineages (5). The foremost question that now emerges is how much the values obtained from these "partially obsolete" immunoassays will reflect *ex vivo* humoral immunity? Although there is no definitive answer to this question, the paramount number of breakthrough infections developing in subjects with considerably high values of anti-SARS-CoV-2 antibodies measured with contemporary immunoassays confirm that many of these immunoglobulins may be actually ineffective against new lineages (6,7). The paradigm here is that the high degree of "analytical" accuracy that the current immunoassays display when measuring the concentration of anti-SARS-CoV-2 antibodies does not necessarily go hand in hand with their "clinical" accuracy to reflect *ex vivo* neutralization (*Figure 1*).

This evidence paves the way to a compelling need of rethinking the current approach used to assessing humoral immunity. Although kit reformulation with novel recombinant antigens may provide a temporary solution, thus generating more robust and updated information on anti-SARS-CoV-2 neutralizing antibodies, this may turn also as an almost wasted effort when new SARS-CoV-2 variants will emerge, since there is a concrete likelihood that these new lineages will display antigen structure and/or conformations characterized by sufficient diversity from

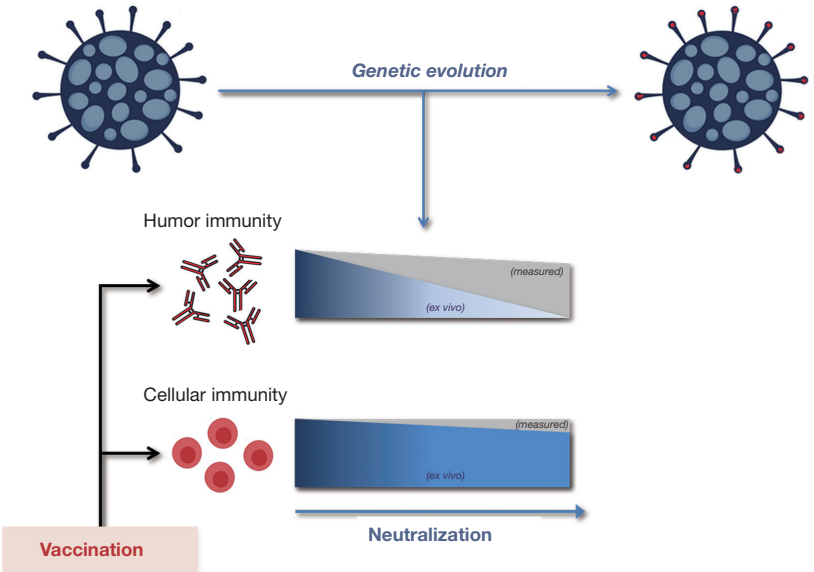

Figure 1 Long-term evolution of humoral and cellular immunity against SARS-CoV-2. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

those included in the reformulated kits (8), thus bringing us again to the same starting point. Given the rapid genetic diversification of SARS-CoV-2, the diagnostic industry is indeed incapable to sustain (at least for repeated long periods) near constant kit reformulation.

Is cellular immunity the key?

Before specifically addressing the important role of cellular immunity in viral diseases, thus including COVID-19, we should consider that the current generation of COVID-19 vaccines has been developed using the sequence of the prototype SARS-CoV-2 virus, which seems now considerably different from that of the circulating Omicron variants (9). Thus, serious concerns have been raised that even the fourth dose of the mRNA-based vaccines may not sufficiently boost humoral protection against omicron variants, in that the neutralizing potency of booster-elicited antibodies may not be accompanied by enhanced neutralization of these diverging lineages (10) (*Figure 1*). In line with these findings, an ongoing study in healthcare workers recently revealed that a fourth dose of a mRNA based COVID-19 vaccine was effective to restore serum anti-SARS-CoV-2 antibody levels to the values seen after the third dose, though this humoral response was only marginally effective for preventing the development of Omicron infection and mild COVID-19 illness. This is not an isolate report. since as we discussed earlier, we are now observing an increasing number of breakthrough cases all around the world even in people with robust levels of anti-SARS-CoV-2 antibodies (11,12). Importantly, the suboptimal protection of the fourth vaccine dose seems also to be accompanied by an enhanced burden of local and systemic adverse reactions (i.e., 80% and 40%, respectively) (11), thus emphasizing the need to reassess the balance between benefits, risks and even healthcare costs associated with widespread administration of multiple vaccine boosters.

On the other hand, convincing evidence has now been provided that the waning protection against asymptomatic or mildly symptomatic COVID-19 illness seems not accompanied by a parallel decline in protection against severe disease, which remains around 70% several months after completing the primary vaccination cycle, even when serum anti-SARS-CoV-2 antibodies levels have considerably decreased (13). A possible explanation has been provided by a number of studies which addressed the efficacy of cellular immunity against highly mutated SARS-CoV-2 lineages, such as Omicron, all concordant in revealing that COVID-19 vaccination elicits a degree of cellular immunity which seems capable to cross-recognize a multitude of SARS-CoV-2 variants, including Omicron (14-16). Interestingly, another recent study published by Jung and co-authors evidenced that BNT162b2 vaccine-elicited memory T cells displayed a considerable response

against the spike protein of the Omicron lineages, with no major differences among subjects who received two or three vaccine doses (17). It can hence be reliably underpinned that the persistent protection against severe and/or critical COVID-19 illness elicited by primary vaccination and/or following the first vaccine booster administration may be substantially attributable to cellular rather than to humoral immunity (*Figure 1*). More specifically, the gradual decrease of efficient neutralizing antibodies against new and highly mutated variants would explain the increasingly higher risk of being infected and developing mild disease (mostly represented by an influenza-like syndrome), with symptoms prevalently localized in the upper respiratory tract (18), whilst a conserved cytotoxic activity of the T cells would impede the infection to propagate. In keeping with this assumption, it seems not so illogical to suggest that monitoring cellular immunity may currently provide more useful information than measuring anti-SARS-CoV-2 antibodies for purposes of vaccine prioritization. That said, it can not be excluded that the reduction in disease severity with Omicron may be substantially attributable to alterations in intrinsic viral properties, as opposed to a function of cellular immunity. Moreover, the role of cellular immunity at the mucosal level in preventing infection still requires further investigation. However, further and broader monitoring of cellular immunity in the general population may help answer these questions and drive public health guidance through the next stages of the pandemic.

Conclusions

Although the efficacy of the second COVID-19 vaccine booster for preventing mild Omicron infections remains uncertain in the general healthy population, we cannot feasibly continue to boost antibody responses forever (12). Studies like that published by Torres *et al.* (19) revels that it is now challenging to identify threshold values of anti-SARS-CoV-2 neutralizing antibodies (measured with current immunoassays) displaying sufficient protect against highly mutated variants, including those belonging to the Omicron lineage, so that infection will likely occur regardless of the amount of neutralizing antibodies. The risk of misinterpreting laboratory data is further increased if one considers that some current anti-SARS-CoV-2 spike protein immunoassays may be unreliable for characterizing the serological response after infection with Omicron or other lineages containing several mutations in the spike protein moiety, as preliminary data published by Springer *et al.* have recently confirmed (20).

Rather than simply focusing on administering multiple doses of the current COVID-19 vaccines, whose benefits remain substantially speculative for the general population (21), important evidence is now emerging from trials based on new vaccine (chimeric) formulations, constructed according to the sequence of recently emerged variants of concerns. A recent pilot study using a Delta-Omicron SARS-CoV-2 chimeric receptor binding domain (RBD) dimer evidenced that this new vaccine elicited a much better protection against infections from both Delta and Omicron variants in mice, by considerably reducing both viral load and the risk of developing symptomatic illness (22). The concrete perspective of pursuing "hybrid" SARS-CoV-2 immunity, for example through "seasonal vaccination", requires huge organization and economic efforts, but is not a real novelty, as this practice has become virtually commonplace for counteracting the antigenic drift of influenza viruses (23).

Nonetheless, the possible translation of this straightforward concept into long-term management of COVID-19 leads the way to important perspectives for laboratory diagnostics. The constant monitoring of anti-SARS-CoV-2 antibodies levels with "obsolete" immunoassays may turn to be unsuccessful, or even misleading, since it may instill a false sense of reassurance to people with extremely high antibodies titers who, instead, may only be marginally protected against COVID-19 illness (*Figure 1*). Contrarily, major efforts should be focused to construct efficient assays aimed at deciphering and monitoring *ex vivo* cellular immunity, since this approach may be more robust to withstanding SARS-CoV-2 antigen drift and reflecting *ex vivo* vulnerability to COVID-19. Some of these assays have already become commercially available (24,25), even if their real performance remains undetermined (26), thus paving the way to additional research on this matter.

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