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Implications of defective immune responses in SARS-CoV-2–vaccinated organ transplant recipients

Effective vaccines against viruses, including vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), induce virus-specific immune memory composed of cellular and humoral components that together prevent infection after exposure to the virus; however, many of these responses are compromised in solid organ transplant patients. Initial T cell and B cell activation in response to any immune stimuli, including vaccines, requires innate immune activation signals commonly transmitted by pathogen-associated molecular patterns ligating pattern recognition receptors expressed on various immune cells. Subsequently, vaccine-induced protective humoral immunity requires collaborative interactions between subsets of CD4⁺ T cells, including follicular helper T cells (T_{FH}), and activated B cells within germinal centers (GCs), a process that results in production of memory CD4⁺ T cell populations, as well as high-affinity, memory B cells and long-lived, antibody-secreting plasma cells. In addition, effective vaccines induce expansion and differentiation of antigen-specific, memory CD8⁺ T cells that can rapidly develop into effector cytotoxic lymphocytes capable of killing virus-infected cells. Emerging evidence indicates that differentiation of memory CD8⁺ T cells proceeds through requisite intermediaries including a highly proliferative stem-like memory CD8⁺ progenitor cell. Key features that distinguish immune memory from the naïve state include (i) elevated frequencies of antigen-specific T cells, B cells, and antibody-secreting cells; (ii) increased antibody affinity for target antigen; and (iii) the ability to more rapidly respond to the inciting stimulus. Multiple vaccine doses can boost the primary response induced by the initial vaccination by providing supplementary innate immune activation signals, by promoting further expansion of previously T and B cell clones activated by the initial vaccine, and by promoting GC responses that further enhance antibody affinity maturation and antibody production.

Inherited or acquired defects in any of these interrelated immunological processes could potentially disrupt development of protective immunity in response to the vaccine, especially the SARS-CoV-2 vaccines. In a recent issue of *Science Immunology*, Rincon-Arevalo and colleagues add to the emerging literature documenting

that one specific at-risk population for SARS-CoV-2 vaccine failure is organ transplant recipients (1). Transplant recipients require life-long immunosuppression regimens, which commonly include some combination of a calcineurin inhibitor (such as tacrolimus), a steroid, and/or an anti-metabolite [such as mycophenolic acid or mycophenolate mofetil (MMF)]. These regimens nonspecifically inhibit T and B cells to prevent rejection of the transplanted organ, but also have well-documented and anticipated off-target effects including an increased risk of infection and malignancies. Several publications from 2021 have now documented that immunosuppressed transplant recipients do not routinely develop protective antibody titers after full vaccination with any of the approved SARS-CoV-2 mRNA (2) or viral vector (3) vaccines. Associative evidence suggests that use of MMF, an anti-proliferative agent that affects T and B cells, contributes to the lack of response (1, 2). A more detailed understanding of the immunosuppression-induced defects after SARS-CoV-2 vaccination is needed to guide new approaches to induce protective immunity in this at-risk population.

Expanding upon published data, Rincon-Arevalo and colleagues show that the absence of protective immunoglobulin G in vaccinated kidney transplant recipients (KTRs) associates with defects in frequencies of receptor binding domain (RBD)–specific, class-switched B cells, circulating plasmablasts, and proliferating lymphocyte (including TCF7⁺CD27⁺GZMK⁺ stem-like CD8⁺ T cell memory precursor) subsets compared with healthy controls (1). These observations suggest that multiple components of the immune response required for protective antibody production are impaired in KTRs after vaccination against SARS-CoV-2. Analogous analyses of dialysis patients revealed delayed, but not absent, protective immunity after vaccination, supporting the conclusion that the immunosuppression (rather than the kidney disease) is likely the etiology of the observed defects in the KTRs. While the authors did not specifically analyze RBD-specific T cells in any of the subjects, the diminished numbers of proliferating CD8⁺ T cells suggest that KTR may not develop protective T cell immunity after vaccination.

These disappointing findings have significant clinical implications on two levels. At the individual level,



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current methods may not achieve adequate protection for those on immunosuppression; this concern is supported by emerging reports (4) of a higher-than-expected rate of breakthrough SARS-CoV-2 infections (including the highly infectious delta variant) in transplant patients. As such, transplant patients must sustain infection control measures, and medical treatment must continue to rely on passive immune antibody transfer until effective vaccine regimens are developed. Although antibody testing is commercially available, correlates of protective immunity remain unknown in both immunocompetent individuals and those taking immunosuppression (with likely suboptimal T cell responses as well), so all transplant recipients, regardless of antibody levels, should be counseled to “act unvaccinated” until protective immunity is better understood. At the population level, transplant recipients who have failed to achieve adequate protection may create a reservoir for continued viral spread and importantly for ongoing mutation; with around 500,000 transplant patients alive in the United States today, and many more worldwide, this could have a substantial impact on public health.

These findings also help prioritize the next wave of research and development of SARS-CoV-2 vaccination strategies in transplant recipients. Although antibody levels are emerging as correlates of protection in healthy individuals, there is still an urgent need to understand the relative contribution of humoral and T cell immunity in conferring protection. In particular, it is important to understand whether the CD8⁺ T cell response in the absence of antibody confers full, partial, or no protection in transplant patients who have received a SARS-CoV-2 vaccine. Validated biomarkers of protection are also needed in both immunocompetent and immunosuppressed populations. A more granular understanding beyond antibodies is crucial for individual assessment and clinical decision-making, as well as for assessment of trials seeking to confer protection against SARS-CoV-2 in transplant patients and other immunosuppressed populations.

Although the immunology literature supports efficacy of booster vaccines, and booster doses of SARS-CoV-2 vaccines have been reported to augment protective antibodies in a handful of transplant patients (5), it is important to emphasize that these approaches have not been tested rigorously in clinical trials, that the impact of boosters on T cell immunity has not been determined, and that this relatively simple strategy was not successful in all patients. Additional boosters, boosters of another class of vaccine, or higher-dose boosters may rescue more patients, although others may require immunosuppression modulation to develop full protective responses. These escalating approaches entail increasing risk of T cell- or

antibody-mediated injury to the allograft, which may not be reversible. Hence, clinical trials performed in controlled settings with careful allograft monitoring are required; these trials should be rigorous but rapid, and adaptive methodology might help with efficiency.

The global scientific response to the SARS-CoV-2 pandemic has been a marvel, from the identification of an unknown virus, the development of new diagnostics, immune monitoring, and vaccines, to unprecedented global mass vaccination within a year. However, vulnerable populations remain, and there is no time to rest in the last mile. The full force of scientific effort is still needed to provide immune protection for those who remain at risk from this deadly virus and to control the reservoir to prevent fertile fields for mutations that put the entire population at risk.

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