COVID-19

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Illuminating a blind spot in SARS-CoV-2 immunity

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Indigenous populations are disproportionately affected by COVID-19, but are rarely studied. An investigation of the immune response of Australian First Nations people to SARS-CoV-2 vaccination and infection shows a major effect of comorbidities.

In research, as in life, it is easy to forget that we have blind spots — realities that take place outside of our field of perception. The COVID-19 pandemic has afflicted the entire world, but not all communities have been affected to the same degree. The disease burden has been noticeably more severe among Indigenous populations, irrespective of their location. Pueblos in New Mexico Tribal Lands, Indigenous communities in Brazil, and Australian First Nations people have all encountered greater COVID-19-related morbidity and mortality than non-Indigenous populations in the same geographies[1–3]. However, the immunopathology of SARS-CoV-2 infection has been studied almost exclusively in non-Indigenous populations. In this issue of *Nature Immunology*, Zhang et al.[4] investigate in detail the immune response to SARS-CoV-2 vaccines and infection in Australian First Nations people, comparing it with the response in non-Indigenous individuals. Their results show that overall immune responses are robust and broadly similar in both groups, and that the presence of comorbidities — with a higher prevalence among the Indigenous participants — explains the observed differences in disease burden[4].

The immune response to SARS-CoV-2 — including the immunity that is generated after infection and the protection that is acquired following vaccination or through hybrid immunity (a combination of vaccination and natural infection)[5] — has been instrumental in reducing the global disease burden. Although the protection against infection wanes progressively over time[6], protection against severe outcomes, namely hospitalization and death, is more stable[7]. Consequently, investigation of the capacity of Australian First Nations people, who encounter a greater disease burden, to generate immune responses following SARS-CoV-2 vaccination or infection is of great importance.

Zhang et al.[4] studied 97 individuals (58 Australian First Nations people and 39 non-Indigenous people) at multiple times before and after vaccination with the anti-SARS-CoV-2 mRNA vaccine BNT162b2. Seroconversion levels and the dynamics of IgG antibodies, including neutralization, were similar in both groups, although peak IgG titers against the receptor-binding domain of the viral spike protein were slightly lower in Australian First Nations people. Overall, $CD4^+$ T cell and $CD8^+$ T cell responses were also robust and comparable in the two groups, indicating that the immune response elicited by this vaccine is very similar across Australian First Nations and non-Indigenous people.

However, Zhang et al.[4] also observed that the post-vaccination peak IgG titers against the ancestral and Delta variants were slightly but significantly lower in Australian First Nations people than in non-Indigenous individuals (Fig. 1). When they tried to dissect the reasons for this quantitative difference on the basis of clinical or demographic variables, their interesting finding was that the presence of comorbidities was the key feature affecting the difference

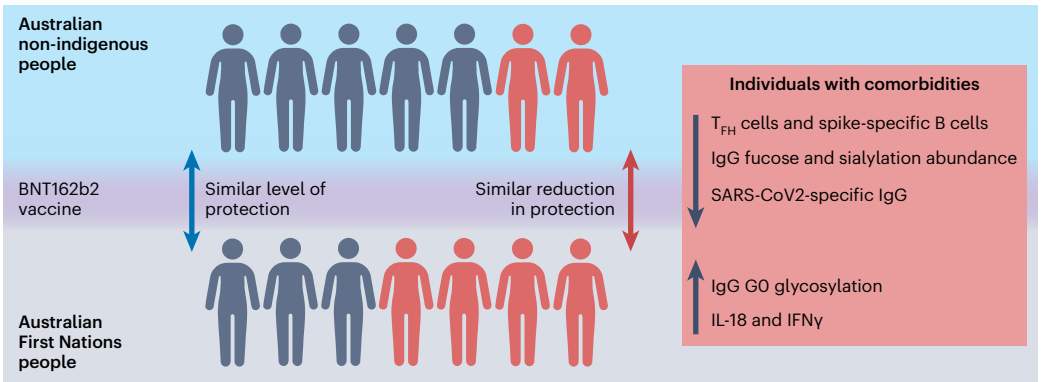

Fig. 1 | Comorbidities drive poor antibody responses against SARS-CoV-2 among Australian First Nations people. Zhang et al.[4] have found that the humoral response elicited following vaccination with the COVID-19 mRNA vaccine BNT162b2 is reduced among Australian First Nations people when compared with non-Indigenous individuals. Nevertheless, the same level of overall protection is observed when comparing individuals without comorbidities from both groups (blue), and when comparing individuals with chronic diseases from the two populations (red). The greater frequency of individuals with comorbidities among the Australian First Nations people explains the overall reduced response when the population is assessed globally. Individuals with comorbidities display more pro-inflammatory mediators (namely IL-18 and IFNγ) and perturbation of IgG glycosylation (G0). These findings correlate with a reduced frequency of T follicular helper (T_{FH}) cells and spike-specific B cells, in line with the production of reduced amounts of SARS-CoV-2-specific antibodies.

in peak antibody titers. Indeed, Australian First Nations participants with comorbidities (39%) had significantly lower IgG titers than First Nations people without comorbidities (Fig. 1). Moreover, the latter had peak titers that were similar to those of non-Indigenous people, who (with one exception) did not report comorbidities. Zhang et al.[4] delved further and found that one of the main differences in the immunity of Australian First Nations people and non-Indigenous people was a change in the pattern of antibody glycosylation, producing a higher level of glycosylated IgG G0 in the former, particularly in people with comorbidities. G0 glycosylated antibodies are known to be pro-inflammatory, and in this study they correlated with the plasma levels of the pro-inflammatory cytokine interleukin-18 (IL-18). Finally, Zhang et al.[4] replicated the findings of lower IgG titers, elevated IgG G0 glycosylation and elevated IL-18 levels in another cohort of vaccinated non-Indigenous people with comorbidities ($n = 69$), who showed a pattern resembling that observed in Australian First Nations people with comorbidities (Fig. 1). In fact, in a multivariable model that included comorbidities, glycosylation levels, Indigenous status, age, gender and body mass index (BMI), only the comorbidities and BMI were important predictors of IgG titers. In contrast to these findings regarding humoral immune responses, cellular responses were not grossly affected by the presence of comorbidities.

It may seem counterintuitive that individuals with comorbidities that lead to the expression of more inflammatory mediators displayed a poorer humoral response. Although the precise explanation for this observation is still elusive, it has been described that chronic pathologies can lead to a state named 'inflammaging', characterized by systemic subclinical chronic inflammation, which is a hallmark of aging. It is well documented that poor humoral responses to infection and vaccination are common among the elderly. It has also been reported that Brazilian populations living in endemic areas of chronic infectious diseases display features of inflammaging, accelerated senescence and dysfunctional immunity[8]. An alternative hypothesis concerns the developmental bifurcation of activated T cells towards type 1 helper T (T_H1) cells or follicular helper T (T_{FH}) cells[9]. This process is tightly regulated by inflammatory cytokines, namely IL-2, that favor T_H1 cell polarization at the expense of the T_{FH} cell fate[10,11]. In fact, the Australian First Nations people with impaired humoral responses displayed a coordinated reduction of SARS-CoV-2-specific antibodies and T_{FH} cells (Fig. 1), but without an equivalent defect in cellular responses[4].

The finding that, in individuals without comorbidities, the immune response to SARS-CoV-2 vaccination is similar in Australian First Nations people and the non-Indigenous population is a refreshing reminder that, ultimately, all human beings share a similar immune capacity. However, the large impact of comorbidities on immune function among Australian First Nations people raises important concerns. The significance of this finding in explaining the large impact of COVID-19 on Australian First Nations people may extend beyond the high prevalence of comorbidities among Indigenous populations when compared with non-Indigenous ones. It is likely that individuals with good access to healthcare will maintain better control of their comorbidities compared with individuals with the same comorbidities but with social, geographical and financial barriers that reduce their access to healthcare. Whether good control of comorbidities will restore a full-fledged immune response is not clear. Indeed, the group sizes in the study by Zhang et al.[4] were underpowered to allow this type of assessment.

It is a challenge for regulatory authorities to consider the characteristics of population groups not represented in clinical trials in their recommendations[12]. It is therefore important to obtain scientific information that may complement those trials to provide support for measures specific to individuals who may respond suboptimally to standard regimens. Regarding vaccination, this was the case for immunosuppressed people and may also apply to underserved Indigenous populations. Altogether, the work by Zhang et al.[4] work is a welcome addition to our understanding of immune responses to vaccination, and a reminder that the study of populations that are not often the subject of scientific investigations can have important general implications. It is, therefore, essential for the research community to avoid blind spots regarding those populations that are poorly represented in the scientific record, and to take into account the impact of health determinants on top of human biology.

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Competing interests

The authors have no competing interests.