Motif chemokine 5) was enriched in macrophages isolated from the wound bed. CCL5 promotes inflammation by recruiting other immune cells to the tissue, and its expression is increased in individuals with IBD (11, 12). Wound healing was not impaired by D. hansenii colonization in mice in which Ccl5 was deleted. Culture of macrophages with D. hansenii followed by RNA sequencing revealed that activation of the type I interferon–CCL5 pathway in macrophages prevents wound healing (see the figure).

D. hansenii is likely not a common resident of the gut, because it was isolated from all samples obtained from individuals with IBD but from only 1 of 10 healthy donors. D. hansenii is an environmental yeast that is distinctive in its ability to tolerate high-salt and pH conditions and is often used in cheese and meat production (13). It is possible that the ability of D. hansenii to persist in extreme environments also allows it to survive within inflamed tissue. This suggests that certain dietary recommendations could be made for patients with IBD to prevent colonization with D. hansenii, but this would need to be established with clinical trials. Additionally, use of antibiotics in individuals with chronic intestinal disease should be evaluated more carefully. The study of Jain et al. demonstrates that the loss of commensal microbes can open up niches for potentially harmful opportunistic organisms. Although CCL5 represents an attractive drug target that is currently being explored in IBD patients (14), it is one of many factors that is dysregulated during disease. Because commensal microbes can influence multiple host pathways that include preventing inflammation (15), colonization of pathogens, and promoting wound healing, specific cocktails of commensal bacteria might prove to be better therapeutic agents that act on several levels to protect from disease.

REFERENCES AND NOTES

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**CORONAVIRUS**

Immunity to SARS-CoV-2 variants of concern

Variants show variable escape from vaccine immunity, but residual protection may suffice

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Vaccine candidates based on spike, the glycoprotein that is essential for host cell entry by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were being designed within days of its reported sequence in January 2020. All the vaccines aim to prevent disease primarily (but not exclusively) by eliciting neutralizing antibodies that block spike and therefore prevent the ability of SARS-CoV-2 to infect cells. The 95% efficacy of the BNT162b2 messenger RNA (mRNA) vaccine (from Pfizer/BioNTech) heralded a series of results showing that eliciting neutralizing antibodies to spike strongly correlated with protection from disease in clinical trials of various vaccines. Currently, there is concern about reduced vaccine-induced immune protection to emerging variants that have mutations in the spike protein. On page 1152 of this issue, Muirk et al. (1) found reduced induction of neutralizing antibodies from BNT162b2. However, there is likely sufficient efficacy remaining to confer protection from symptomatic disease.

Coronaviruses are very large and complex compared with other RNA viruses (around four times the size of the hepatitis A virus genome), and their replication fidelity must therefore be higher. Despite this, once a pathogen has been allowed to infect more than 100 million people, it is not a surprise that sequence variants with a selective advantage emerge. Toward the latter part of 2020, just as regulators were granting approvals to a series of vaccines based largely on the wild-type “Wuhan” sequence spike antigen, several SARS-CoV-2 “variants of concern” were detected. These variants have potentially enhanced transmission, pathogenicity, immune escape, or a combination of all three.

The first sequences of a variant of concern that emerged in the UK, B.1.1.7 (also called 501YVI), emerged in September 2020. It includes eight amino acid changes within spike. One of these, N501Y (Asn501→Tyr), increases the affinity of spike for its cellular target angiotensin-converting enzyme 2 (ACE2) and, together with other less well characterized mutations, has resulted in enhanced transmission (recognized since December) and possibly enhanced pathogenicity. Might this variant also escape antibody-mediated immunity? Muirk et al. examined the ability of immune sera from 40 older or younger two-dose BNT162b2 vaccine recipients for neutralization of a pseudotype virus (a safe, surrogate virus engineered to express spike) carrying wild-type sequence spike or all of the B.1.1.7 spike mutations. The sera had a wide range of neutralizing antibody titers measured against the wild-type spike, from around 1/50 to around 1/1200. Although there was a significant reduction in geometric mean titers for the younger (though not the older) cohort against the B.1.1.7 variant, the authors argue that on the basis of our understanding of other respiratory viruses such as influenza virus, an overall reduced titer of some 20% would not be predicted to meaningfully reduce vaccine efficacy. However, such findings confirm that the B.1.1.7 spike mutations affect not only transmission but also immune recognition.

Another study looked in considerable detail at potential vaccine escape by B.1.1.7 (2). They considered immune sera from 23 vaccinees with a median age of 82, analyzed 3 weeks after a single dose of BNT162b2. Using a pseudotype virus carrying spike with all eight mutations led to a sixfold reduction of neutralization for the majority of sera. In this older cohort, the ablation of functional neutralization was more apparent in those starting with lower antibody titers to the wild-type sequence spike. A parallel dataset for pseudotype neutralization of wild-type sequence or B.1.1.7 spike by mRNA-1273 (Moderna) or NVX-CoV2373 (Novavax) vaccine sera detects a more marginal reduction in activity against the variant (3).

When population variation can mean that people develop diverse neutralizing antibody titers after vaccination, the extent to which a small drop in neutralization endangers...
protection from symptomatic disease depends to some extent on the immunogenicity of the vaccine and how much margin it leaves for protection. This issue is starting to be addressed through analyses of ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca) vaccinees in the UK (4). Although neutralizing antibody titer against B.1.1.7 was reduced approximately ninefold (from a mean of about 1/500 neutralizing antibody titer against wild-type virus), this did not affect vaccine efficacy because there was no enhanced susceptibility to infection [as determined with polymerase chain reaction (PCR) testing] attributable to the variant among the 499 participants who became infected.

Although the B.1.1.7 variant has had massive impact in exacerbating case-load and severity across many countries, there is even greater concern about variants that carry additional immune evasion mutations, notably the E484K (Glu484→Lys) mutation found in the B.1.351 (501Y2) variant that emerged in South Africa, the P1 variant found in Brazil, and sporadic examples from UK sequencing that show E484K on the B.1.1.7 background (5). That the immune evasion mutations—K417N (Lys417→Asn), E484K, and N501Y—can arise in evolution experiments in vitro involving culture of SARS-CoV-2 in the presence of immune sera offers caution against suboptimal vaccination regimens (6).

Concern about the B.1.351 variant derives from analyses of its effects on neutralization activity. The variant shows substantial ablation of any virus-neutralizing activity of therapeutic monoclonal antibodies (mAbs) (7). Preliminary data suggest a reduced neutralizing response in sera from ChAdOx1 nCoV-19 vaccinees and reduced efficacy in preventing mild to moderate COVID-19 (8). This supports the view that neutralizing antibody titer is the key correlate of protection (CoP). Although analysis based on loss of in vitro neutralizing activity by individual mAbs representing the three dominant classes of epitopes on spike offers strong evidence for immune evasion by the variants, the effect is less pronounced at the level of polyclonal immune serum after convalescence or vaccination. This suggests that the neutralizing repertoire is broader and more resilient than so far documented.

Findings from studies with mAbs offer caution for using these therapeutically, given their vulnerability to loss of individual epitopes and also their ability to drive selection of variants that can evade immune recognition. Of course, the flip side of this argument is that detailed mapping of the neutralizing antibody epitopes in spike can facilitate the design of broadly neutralizing vaccines and mAbs that can target numerous spike mutants (9). It has been posited that SARS-CoV-2 may continue to accumulate mutations that evade immune responses (10). But as previously explored for other viruses, such as HIV, immune evasion often comes at a biological fitness cost to the virus, tending to impose an upper limit to the number of mutations that can be afforded when faced with a broad, neutralizing antibody repertoire (11).

Additionally, given that similar mutations arise recurrently in spike, presumably through convergent evolution in geographically distinct isolates, it is possible that the spike variants offering a survival advantage to the virus will be constrained and finite. Furthermore, a spike protein that mutates residues A, B, and C to evade antibody recognition runs the structural risk of generating a new neutralizing epitope, D. Therefore, a finite number of iterative vaccines could target key variants, but this would not necessarily have to be reaped annually as with influenza virus vaccines. Seasonal “common cold” human coronaviruses tend to appear with 2-year cycles, and recent data for one of these suggest that antigenic drift (mutations that undermine immune recognition) may underlie escape from acquired immunity (12).

T cell immunity is likely to feature as an additional CoP against COVID-19 (13). The CD4+ and CD8+ T cell response encompasses specificity to several hundred epitopes across the entire SARS-CoV-2 proteome, the majority of which are unimpaired in the variants (14, 15). Even those T cell epitopes that are altered in the SARS-CoV-2 variants will in most cases bind to the different human leukocyte antigen (HLA) molecules that present antigenic peptides to T cells, although binding affinities may be altered. It would be helpful to investigate whether T cell immunity is modified by the SARS-CoV-2 variants.

The assessment of variants on neutralization are complicated by the variability of pseudotype assays used in these studies. It would be helpful to have standardized live-virus in vitro neutralization assays as internationally comparable reference points. As ever, these are discussions that must be tethered to some sense of CoP values. Although much debated, many researchers have the sense that people with a neutralizing antibody IC50 (half maximal inhibitory concentration) greater than ~1/100 serum dilution would likely be safe from infection, or at least from symptomatic infection. Given that these are highly potent vaccines that often induce neutralizing antibody responses with IC50 of at least 1/1000, there is hopefully a reasonable safety margin before reduced recognition of variants means that effective protection is lost (see the figure). Ultimately, the best defense against emergence of further variants of concern is a rapid, global, vaccination campaign—in concert with other public health measures to block transmission. A virus that cannot transmit and infect others has no chance to mutate.

**REFERENCES AND NOTES**
