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SARS-CoV-2 B cell receptor signatures in risk populations

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Commentary In-Press Preview

Many individuals possess B cells capable of recognizing epitopes on the spike glycoprotein of SARS-CoV-2. In this issue of the *JCI*, Paschold and Simnica et al. interrogated the frequency of SARS-CoV-2–specific B cell receptor rearrangements in healthy subjects based on age and cancer status. The authors found that, while SARS-CoV-2–specific antibody signatures can be identified in the repertoires of young, healthy individuals, such sequences are less frequent in elderly subjects or cancer patients. Overall, this study sheds light on B cell repertoire restrictions that might lead to an unfavorable clinical course of COVID-19 infection in risk populations.

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Abstract

Many individuals possess B cells capable of recognizing epitopes on the spike glycoprotein of SARS-CoV-2. In this issue of the *JCI*, Paschold and Simnica et al. interrogated the frequency of SARS-CoV-2–specific B cell receptor rearrangements in healthy subjects based on age and cancer status. The authors found that, while SARS-CoV-2–specific antibody signatures can be identified in the repertoires of young, healthy individuals, such sequences are less frequent in elderly subjects or cancer patients. Overall, this study sheds light on B cell repertoire restrictions that might lead to an unfavorable clinical course of COVID-19 infection in risk populations.

Older age and other risk factors

The ongoing coronavirus disease 2019 (COVID-19) pandemic is caused by the novel human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While it appears that elderly individuals are similarly susceptible to SARS-CoV-2 infection as younger individuals, the severity and mortality of COVID-19 are higher in older individuals (1). There are several explanations as to why the older age group has a higher risk of COVID-19 severity and mortality. First, some individuals may have more comorbidities as they age, such as having a history of myocardial infarction, chronic pulmonary disease, congestive heart failure, or liver disease. The cumulative effect of such comorbidities in elderly individuals can increase the risk of severe COVID-19 and death (2). Alternatively, increased severity and mortality of COVID-19 in elderly patients can also be explained by the normal aging of the human immune system (3).

Age and cancer status affects B cell repertoire

The human immune system has the capacity to mount an effective offense against foreign intruders to our bodies. This property of the immune system is, in part, mediated by a large number of unique B and T cells that form the human B and T cell repertoires, respectively. During the course of human life, the immune system undergoes a gradual remodeling and deterioration process referred to as immunosenescence. Immunosenescence has been associated with a reduced B and T cells repertoires as well as a decreased proliferation of lymphocytes (3, 4), leading to higher susceptibility to viral and bacterial infection in older individuals (5). In addition to a diminished capacity to fight infections, older age is also associated with a reduced immune response after vaccination (6), which can be explained in part by restricted clonal diversity of B cell repertoires in the elderly compared to younger individuals (7).

In this issue of the *JCI*, Paschold and Simnica et al. (8) mined the human B cell receptor repertoires to study the impact of age and cancer status on SARS-CoV-2 B cell signatures. In total, the authors analyzed B cell immune repertoire from 68 COVID-19 patients with different disease courses, 200 healthy individuals of all age groups, and 500 cancer patients (236 with hematological malignancies and 264 with solid cancers). By applying diversity measurements such as repertoire richness (which reflects the number of unique B cell clonotypes) and diversity (which reflects the distribution of antibody sequences), Paschold and Simnica et al. (8) found an association between older age and a decreased B cell receptor repertoire richness and diversity (**Figure 1A**), confirming previous studies of B cell sequence diversity in elderly individuals (7). The authors also found that positive cancer status independent of prior treatments results in diminished B cell diversity compared with age-matched healthy subjects (8).

Mining B cell repertoires

Large panels of SARS-CoV-2 neutralizing antibodies have been isolated from COVID-19 patients (9-11). The majority of isolated neutralizing antibodies display a naïve-like phenotype including an unusually low number of somatic mutations. The existence of a large number of germline-like antibodies with strong neutralizing activities suggests that the frequency of SARS-CoV-2–specific B cell precursors displaying B cell receptors that recognize SARS-CoV-2 neutralizing epitopes might play a role in the progression of COVID-19 infection. However, little is known about the frequency of SARS-CoV-2–reactive B cell precursors in the repertoires of elderly or other risk group patients.

Paschold and Simnica et al. (8) profiled B cell receptor sequences of healthy subjects of all age groups and cancer patients using three sets of SARS-CoV-2–specific antibody rearrangements. The first set contained converged sequence clusters obtained from COVID-19 patients with an active infection (12). The remaining two groups included sequences that encoded either neutralizing or non-neutralizing SARS-CoV-2 antibodies from several independent studies (retrieved from the Coronavirus Antibody Database – CoV-AbDab (13)). To determine whether the B cell repertoire restriction observed in elderly individuals and cancer patients is associated with a lower frequency of SARS-CoV-2 antibody signatures, Paschold and Simnica et al. (8) mined B cell repertoires of SARS-CoV-2–infected subjects or individuals who were not exposed to the virus but still possessed sequences that could encode SARS-CoV-2–specific antibodies. While SARS-CoV-2–specific rearrangements were identified among SARS-CoV-2–naive individuals, the frequency of such rearrangements decreased with subjects' age (**Figure 1B**). The likelihood of finding SARS-CoV-2 sequences in cancer patients was also diminished compared with age-matched healthy subjects.

A curious association

Virus-specific neutralizing antibodies mediate the loss of viral infectivity by blocking the entry of the virus into the host cell or interfering with post-entry processes such as membrane fusion or uncoating. Many neutralizing antibodies isolated from COVID-19 convalescent donors target the receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein and prevent the virus from binding to its receptor, angiotensin-converting enzyme 2 (ACE2) (14). RBD-specific neutralizing antibodies were also shown to protect against COVID-19 infection in animal models (15, 16), and several antibodies are currently being developed into COVID-19 therapeutics (17). While SARS-CoV-2 neutralizing antibodies show promise in controlling COVID-19 infection in human subjects (17), the role of non-neutralizing antibodies in the pathogenesis of COVID-19 is less clear. The potential risks of intensified viral infection via antibody-dependent enhancement (ADE) from non-neutralizing antibodies or sub-neutralizing antibodies have been documented for Dengue virus as well as respiratory viruses such as measles and respiratory syncytial virus. ADE can occur through two different mechanisms (18). For viruses that target macrophages, Fc gamma receptors expressed on phagocytic cells can mediate antibody-depended virus uptake resulting in enhanced disease. For viruses that do not infect macrophages, non-neutralizing antibodies can enhance inflammation and immunopathology through the formation of immune complexes or the recruitment of other immune cells. While clinical data do not establish a clear role of ADE during COVID-19 (18), careful evaluation of SARS-CoV-2 vaccine candidates for signs of ADE mediated by non-neutralizing antibodies might be necessary to confirm vaccine safety (19).

Related to the issue of potential ADE effects, Paschold and Simnica et al. (8) mined the human B cell repertoire for the presence of neutralizing or non-neutralizing SARS-CoV-2 rearrangements. While SARS-CoV-2 neutralizing antibody signatures were identified in COVID-19 subjects and control cohorts, SARS-CoV-2 non-neutralizing rearrangements were strongly associated with active COVID-19 cases, a group that contained multiple severe COVID-19 cases. Specifically, Paschold and Simnica et al. (8) found 16 SARS-CoV-2–specific rearrangements in individuals with active COVID-19. Among 16 identified rearrangements, 13 sequences encoded SARS-CoV-2 neutralizing antibodies and 3 sequences corresponded to non-neutralizing antibodies. While neutralizing rearrangements were identified in both fatal and non-fatal cases of SARS-CoV-2 infection, three non-neutralizing sequences were associated exclusively with fatal cases of COVID-19 (**Figure 1C**).

Study limitations

While the frequency of B cell precursors that produce SARS-CoV-2 neutralizing antibodies might influence the disease severity, elderly individuals who had recovered from COVID-19 were found to have high titers of neutralizing antibodies (11). The same study reported slightly higher neutralization activity in hospitalized patients who had a long duration of COVID-19 symptoms (11). Further studies are needed to determine whether the timing of neutralizing response (which can depend on the frequency of SARS-CoV-2–specific B cell precursors) can positively impact disease progression in younger patients. Accordingly, the finding that several non-neutralizing antibody signatures are present exclusively in fatal cases implies, but does not prove, their detrimental role in COVID-19 pathogenesis. It is possible that other immune system markers such as T cell activation or B cell expansion modulate the severity of COVID-19 (20).

Taken together, Paschold and Simnica et al. (8) show that B cell repertoire restrictions in elderly individuals and cancer patients might be responsible for impaired immune response seen in such individuals. Further studies on how SARS-CoV-2–specific B cell precursor frequencies impact COVID-19 disease outcome may provide insights into the prognostic relevance of SARS-CoV-2–specific B cell rearrangements. An open question is whether the restricted nature of the B cell repertoire seen in high-risk groups would allow the development of protective antibody responses against COVID-19 infection.

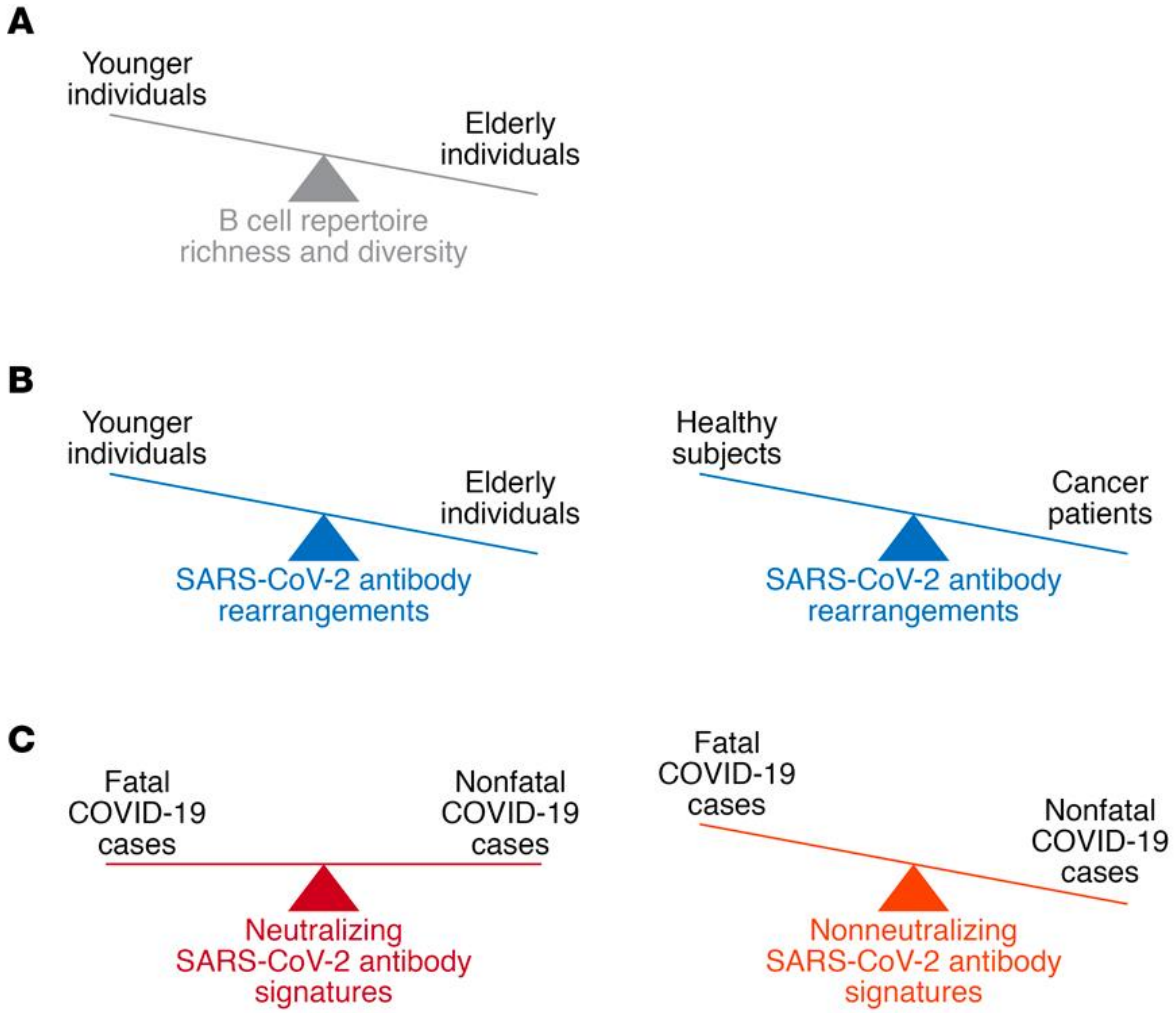

Figure 1. SARS-CoV-2 antibody signatures associate with different risk cohorts. Paschold and Simnica et al. (8) showed: (A) B cell repertoire (grey) was richer and more diverse in younger than elderly individuals. (B) Young and healthy individuals showed a higher frequency of SARS-CoV-2 antibody rearrangements (blue) than those older individuals or those with a cancer status. (C) When compared with neutralizing antibody signatures (red) the frequency of SARS-CoV-2 nonneutralizing antibody signatures (orange) associated with more severe COVID-19.

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