Does common cold coronavirus infection protect against severe SARS-CoV-2 disease?

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The coronavirus disease 2019 (COVID-19) pandemic continues to cause morbidity and mortality. Since SARS coronavirus 2 (SARS-CoV-2) was identified as the cause for COVID-19, some have questioned whether exposure to seasonal common cold coronaviruses (CCCs) could provide tangible protection against SARS-CoV-2 infection or disease. In this issue of the *JCI*, Sagar et al. examined SARS-CoV-2 infections and outcomes of patients who had previously tested positive or negative for CCC infection (CCC⁺ or CCC⁻) by a comprehensive respiratory panel using PCR. No differences were seen between groups in terms of susceptibility to SARS-CoV-2 infection. However, hospitalized patients with a documented history of CCC infection had lower rates of intensive care unit (ICU) admissions and higher rates of survival than hospitalized CCC⁻ patients. While these findings are associative and not causative, they highlight evidence suggesting that previous CCC infection may influence the disease course of SARS-CoV-2 infection.

Common cold coronaviruses

SARS coronavirus 2 (SARS-CoV-2) emerged in 2019 and continues to cause the worldwide pandemic known as coronavirus disease 2019 (COVID-19) (1, 2). Clinical symptoms typically emerge within 2–14 days of exposure and include fever, fatigue, cough/shortness of breath, and sensory (smell/taste) deficits; and in some cases clinical disease can extend to a variety of other organs, including brain, heart, kidney, and gastrointestinal tract (3). In the majority of cases, SARS-CoV-2 infection causes asymptomatic infection or mild/moderate respiratory disease, but in about 10% of cases the clinical disease is severe, requiring hospitalization, with a case mortality rate of 0.5%–1.0% (4). Predisposition to severe COVID-19 is generally skewed to specific subpopulations such as the elderly or those with comorbidities including diabetes, cardiovascular disease, and lung disease. There is substan-tial interest in better understanding the immune response to SARS-CoV-2 to illuminate mechanisms underlying disease predisposition and pathogenesis, and for the development of vaccines and targeted therapies (5, 6).

Common cold coronaviruses (CCCs) are endemic viruses that cause upper respiratory infections with mild to moderate severity (i.e., colds) and include HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63 (6, 7). Combined, this group of four CCCs cause about 15% of the seasonal colds, and host immunity against these viruses is often short lived, so reinfection is not uncommon. Most individuals become infected one or more times by the time adulthood is reached. Since the onset of the pandemic, some have raised questions as to whether previous exposure to CCCs could influence the disease course or severity of COVID-19. In this issue of the *JCI*, Sagar et al. (8) report a possible protective link between prior CCC infection and SARS-CoV-2 disease course. Since most people are likely to have been exposed to CCC in their lifetime, this report assessed the potential role of more recent CCC infection in COVID-19 outcomes. The authors identified patients previously tested for CCCs, and these were grouped as positive and negative for CCC infection (CCC⁺ and CCC⁻). The two groups were studied for SARS-CoV-2 infection and development of severe disease or death. SARS-CoV-2 infection rates were similar in the two exposure groups. However, among hospitalized SARS-CoV-2 patients, the study identified significantly reduced rates of admission the intensive care unit (ICU) for those with prior exposure to CCC infection. Furthermore, hospitalized SARS-CoV-2 patients with prior CCC infection had a higher survival rate compared with the CCC⁻ group (Figure 1). This finding offers some preliminary clinical evidence indicating that prior CCC infection could impact the severity of SARS-CoV-2 infection (8). We speculate that adaptive immune responses, innate immune responses, and other various factors could explain this apparent protective effect.

Adaptive immune response

Cross-reactive adaptive immune responses from previous CCC infections constitute one of the most tangible explanations for this apparent conferred protective effect; and recent reports in the literature support and corroborate the idea of cross-reactivity, at least to a limited extent.

In animal models, T cells (both CD4⁺ and CD8⁺) have been shown to provide effective and protective immunity against coronavirus infection (9, 10). In humans, recent studies point to the possibility of cross-reactive T cell epitopes (especially CD4⁺) between SARS-CoV-2 and CCCs, presumably from previous seasonal infections (11–14). As an example, a recent assay of individuals without SARS-CoV-2

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exposure detected cross-reactive CD4+ T cells that were developed against homologous epitopes in CCC. These cross-reacting cells were present in low amounts and reacted to epitopes that differed from those targeted in COVID-19 patients. The authors of the study speculated that this cross-reactivity could explain, in part, the varied clinical disease spectrum of COVID-19 (11).

Neutralizing antibodies are widely used as a diagnostic marker of previous SARS-CoV-2 infection and serve as COVID-19 therapies (convalescent serum or monoclonal antibody therapies). Their generation at protective levels is the chief goal of many candidate COVID-19 vaccines (15–18). Following SARS-CoV-2 infection in naive individuals, neutralizing antibodies are generated, although they begin to diminish after several months (19). Interestingly, one recent study found that during this convalescent period, a synchronous expansion of cross-reactive antibodies to CCC (HCoV-OC43 and HCoV-HKU1) spike S2, but not spike S1, was generated (16). Antibodies against seasonal CCC are often short lived, but this report (16) suggests that expansion of a preexisting memory response against partially homologous antigens of a related pathogen is possible; whether this memory response provides protection or enhancement of disease remains unknown.

Innate immune response

In humans, severe COVID-19 is reportedly associated with expansion of innate immune cell lineages along with a concurrent reduction in T cell numbers, and protracted by sustained high levels of cytokine expression (20). Previous microbial infection or antigenic exposure has been reported to influence innate immune cell functions — such as cytokine -production and antigen presentation — and this can, in some situations, modulate later infections from another pathogen, part of a process called heterologous immunity (21). In experimental studies, dysregulated or impaired immune responses have been reported as a result of severe coronavirus infection. Specifically, delayed IFN-I signaling early in a mouse model of SARS-CoV infection can lead to expansion of inflammatory monocytes and macrophages and
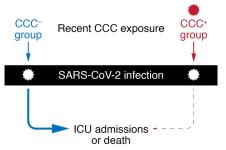

Figure 1. Exposure to common cold coronavirus (CCC) infection may influence the disease course of SARS-CoV-2 infection. Sagar et al. (8) grouped COVID-19 patients according to documented infection with common cold coronavirus (CCC⁻ and CCC⁺). Patients with subsequent SARS-CoV-2⁺ infection were studied to determine whether CCC exposure influenced SARS-CoV-2 disease severity. Previous CCC⁺ diagnosis was associated with reduced ICU admissions and death in hospitalized patients.

elevated lung cytokine/chemokine levels, with vascular leakage and impaired virus-specific T cell responses (22).

Indirect factors

Several factors have been proposed to influence the susceptibility and severity of SARS-CoV-2 infection, often indirectly influencing the immune system. For example, the SARS-CoV-2 virus utilizes angiotensin-converting enzyme 2 (ACE2) as a primary receptor for cellular entry, and the protease transmembrane serine protease 2 (TMPRSS2) serves as a cofactor for this process. Regulation and expression of both ACE2 and TMPRSS2 have been studied as a possible explanation for enhanced SARS-CoV-2 susceptibility and severity in prone populations (23, 24). Similarly, neuropilin-1 was recently shown to bind the cleaved SARS-CoV-2 S1 protein to stabilize virus-receptor interaction for enhanced virus entry and possibly to serve as a coreceptor for the virus (25). Could recent CCC infection dampen the expression of one or more of these factors to diminish the severity of clinical SARS-CoV-2 disease?

Future directions

The study by Sagar et al. (8) potentially opens new avenues of COVID-19 research, but it is important to recognize that the results are still preliminary in nature. Larger, multicenter, prospective studies of diverse populations are needed

to reproduce and validate the results and to clarify the mechanisms involved. Little is known about the T cell response that occurs after CCC infections, and this arm of the immune response could contribute to anamnestic (or recall) immune responses. Future studies could distinguish whether there are specific CCCs that differentially contribute to protection, and determine how the temporal relationship between CCC and SARS-CoV-2 infections contributes to protection or pathogenicity. Furthermore, the CCC⁺ group had more frequent and recent diagnostic testing relative to the CCC⁻ group, suggesting that patients had more clinical respiratory infections (8). These increased episodes prior to SARS-CoV-2 infection could suggest a role for heterologous immunity, wherein previous infection with one pathogen can protect against infection of another pathogen (21). In summary, the connection between previous CCC infection and possible protection against severe SARS-CoV-2 disease is interesting for clinicians and researcher alike. Further validation and mechanistic studies will be required in order to learn how (or whether) this knowledge can be used in prophylactic and/or therapeutic applications.

Acknowledgments

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