bly balanced among males that have mutual friendships than among pairs of males who have one-sided friendships or males that are not friends at all. Also, rates of aggression in males decline with age, and this effect is independent of male dominance rank.

Rosati *et al.* provide convincing evidence that male chimpanzees behave much like humans do as we age, and this pattern might exist in other primates as well (*9, 10*). Thus, the patterns that SST was created to explain appear to generalize beyond our own species and might not depend on having a well-developed concept of time or conscious awareness of mortality. Rosati *et al.* speculated that the patterns in chimpanzees might be influenced by age-related shifts in emotional reactivity (that is, the tendency to experience frequent and intense emotional arousal). Similar mechanisms could operate in humans and be amplified by events that prompt us to contemplate our own mortality.

Similar patterns of age-related changes in social strategies in humans, chimpanzees, and other primates might be the product of evolutionary forces that shape life-history strategies. As individuals pass the age of sexual maturity, their reproductive value steadily declines. This might affect payoffs derived from alternative behavioral strategies. For example, the benefits derived from risky behaviors, such as challenging the top-ranking male for control of the group, are higher for young males than for old ones (*11*). This is reflected in a decline in risk-taking behavior with increasing age in humans (*12*) and other species. For example, the preference of European starlings for risky choices declines as a function of their telomere length, a biological measure of aging (*13*). An evolutionary perspective can provide valuable insights into how natural selection shapes human social behavioral strategies as we grow old. ■

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CORONAVIRUS

Susceptibility to severe COVID-19

Genetic variants and autoantibodies that suppress antiviral immunity are linked to severe COVID-19

By **David B. Beck** and **Ivona Aksentijevich**

The coronavirus disease 2019 (COVID-19) pandemic has led to unprecedented changes in all aspects of our lives and has placed biomedical research at the forefront. One of the many pressing questions surrounding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is identifying the determinants of the clinical spectrum, from people with asymptomatic disease to patients with severe COVID-19. Up to 40% of infections may be asymptomatic, suggesting that a large proportion of people may be protected from disease (*1*). On the other end of the spectrum is severe disease, with an overall estimated fatality rate near 1% (*2*). On pages 422 and 424 of this issue, Zhang *et al.* (*3*) and Bastard *et al.* (*4*), respectively, report analyses of >1600 patients infected with SARS-CoV-2 from >15 countries to identify endogenous factors that determine susceptibility to severe COVID-19.

Many studies have focused on characterizing the heterogeneity of COVID-19 in terms of demographics, with clear evidence of higher mortality in men and older individuals. The adaptive immune system, including both B and T cells, has recently been recognized to play a critical role in providing preexisting immunity to SARS-CoV-2 (*5*–*7*). These studies have highlighted mechanisms that protect against severe symptoms but have not revealed factors that predispose to mortality. Consequently, acquired immune responses to prior infections may account for a large percentage of the variability in disease presentation, although questions remain about additional determinants of disease, such as preexisting comorbidities. Host genetic risk factors have also emerged as a potential explanation for clinical heterogeneity and additionally offer the potential for understanding molecular pathways for tailored therapeutic intervention.

Small-scale studies have implicated the type I interferon (IFN) pathway as protective against SARS-CoV-2 (*8*, *9*). The type I IFN pathway plays a crucial role in mediating innate immune responses to viral infections. This family of cytokines is comprised of 13 IFN-α subtypes, IFN-β, IFN-ω, IFN-κ, and IFN-ε, which all signal through the heterodimeric IFN I receptor, composed of IFN-α/β receptor 1 (IFNAR1) and IFNAR2 (see the figure). In host cells, type I IFNs are expressed at low amounts, poised to combat infections. Upon infection, they are rapidly produced by immune cells, such as macrophages and dendritic cells, to limit the spread of pathogens. In addition, type I IFNs induce the expression of several hundred interferon stimulated genes that can further limit pathogen replication through various mechanisms. However, this typically protective immune response can, when overactivated, lead to autoimmune diseases. Conversely, loss-of-function variants in genes encoding members of the type I IFN pathway lead to severe immunodeficiencies characterized by life-threatening viral infections. Recently, multiple studies demonstrated that impaired type 1 IFN responses may be a hallmark of severe COVID-19 (*10*–*12*), but why this pathway was suppressed remained unclear.

Zhang *et al.* report a large genetic sequencing effort to define host risk factors to SARS-CoV-2 infection, analyzing exome or genome sequences from 659 patients with severe COVID-19 for rare pathogenic variants that could be associated with life-threatening disease. The authors focused on the type I IFN pathway and analyzed 13 candidate genes that have previously been linked with susceptibility to other viral infections. Deleterious variants that can impair gene function were identified in 3.5% (23/659) of cases. Defects in type I IFN gene expression and protein levels were recapitulated in patient cells harboring these variants, demonstrating recurrent diminished activity of this pathway in severe disease. SARS-CoV-2 viral loads were higher in patients' immune cells than in cells from healthy donors (who were infection-negative and seronegative for SARS-CoV-2), demonstrating an inability to properly clear the virus. Together, these data implicate the importance of type I IFN signaling in defense against SARS-CoV-2 infection and suggest that inherited deleterious variants explain a subset of severe COVID-19.

Bastard *et al.* identified neutralizing autoantibodies as another potential cause of severe COVID-19. Autoantibodies recognize and thereby may inhibit host proteins; they

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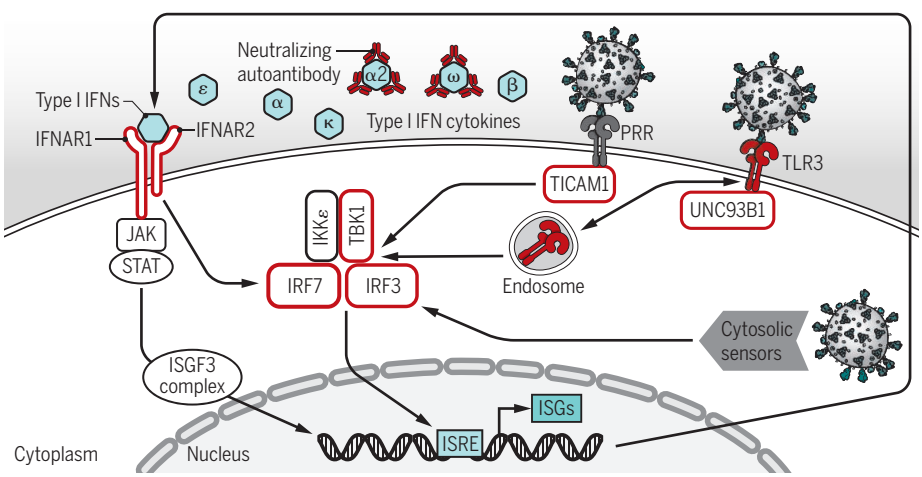
are a hallmark of many autoimmune diseases and are thought to be a contributor to autoimmune pathophysiology. Neutralizing autoantibodies against type I IFNs, mostly IFN-α2 and IFN-ω, were found in up to 13.7% (135/987) of patients with life-threatening COVID-19 and were shown to neutralize activation of the pathway in vitro. By contrast, these autoantibodies were not present in 663 patients with asymptomatic or mild COVID-19 and were only found in 0.33% (4/1227) healthy individuals not exposed to SARS-CoV-2. The presence of neutralizing autoantibodies correlated with low serum IFN-α concentrations. Autoantibodies against type I IFNs were also detected in blood samples of some patients obtained before SARS-CoV-2 infection, indicating that their production was not triggered by the virus in those patients. Notably, inactivating autoantibodies were identified primarily in males (94%) and may be a cause of the higher male-specific disease mortalities.

By analyzing patients with severe COVID-19, these two studies provide evidence that type I IFNs are protective against COVID-19 and that limiting this response through either gene mutations or autoantibodies leads to severe disease. Autoantibodies against other proinflammatory cytokines—including type II IFN (IFN-γ), interleukin-6 (IL-6), IL-17A, and IL-17F—have been reported in healthy individuals, patients with autoimmune diseases, and other opportunistic infections, although the function of these autoantibodies is not always understood (*13*). Studying the mechanisms of acquired immunodeficiency, perhaps related to sex and aging, could help reduce infectious disease morbidity and mortality.

Type I IFN concentrations are tightly regulated, with several rare monogenic autoinflammatory and immunodeficiency disorders caused by either too much or too little interferon production, respectively. Healthy people may have impaired type I IFN responses owing to inherited loss-of-function variants in genes encoding components of the type I IFN signaling cascade but remain clinically silent until they encounter particular viruses or other microbes (*8*). This may be the case in severe COVID-19 patients who have no prior history of clinical immunodeficiency.

Viral sensing by the type I interferon pathway

Viral particles are sensed by various PRRs, including cytosolic sensors. Type I IFNs are potent antiviral cytokines produced by innate immune cells. They bind a specific cell-surface receptor and signal through the JAK-STAT pathway to induce expression of ISGs that encode other antiviral proteins and various transcription factors. Subsets of patients with severe COVID-19 have loss-of-function genetic variants in several members of the type 1 IFN pathway (red) or neutralizing autoantibodies against type I IFNs, specifically IFN-α2 and IFN-ω.



COVID-19, coronavirus disease 2019; IFN, interferon; IFNAR, type I IFN receptor; ISG, IFN-stimulated gene; IKKε, inhibitor of nuclear factor κB kinase subunit ε; ISRE, IFN-stimulated response element; IRF, IFN-regulatory factor; JAK, Janus kinase; PRR, pattern recognition receptor; STAT, signal transducer and activator of transcription; TBK1, TANK-binding kinase 1; TICAM1, TIR domain–containing adapter molecule 1; TLR, Toll-like receptor.

Collectively, this work has important therapeutic implications. Inhaled IFN-β and systemic antiviral therapies are being studied for COVID-19 in clinical trials (*14*). The studies of Zhang *et al.* and Bastard *et al.* offer a potential avenue for identifying people who are at risk of developing life-threatening SARS-CoV-2 infection, primarily older men, by a presymptomatic screening of their blood samples for type I IFN autoantibodies. Identification of such patients may also be important to avoid potential therapeutic use of their convalescent plasma (which will contain the cytokine-neutralizing autoantibodies) in ongoing clinical trials. Furthermore, recombinant IFN-β treatment may not benefit patients with neutralizing autoantibodies, whereas it may work well for patients who carry loss-of-function variants in type I IFN genes, other than *IFNAR1* or *IFNAR2*. In patients with autoantibodies, treatment with IFN-β may be beneficial because neutralizing autoantibodies against this cytokine appear to be less common (*4*, *14*). Findings from these studies have paved the way for precision medicine and personalized treatment strategies for COVID-19.

What remains unknown are the contributions of genetic variation outside of the type I IFN pathway for defense against SARS-CoV-2 infection. Additionally, although Zhang *et al.* focused on rare germline variation, the roles of common single-nucleotide polymorphisms (SNPs) and acquired somatic mutations in immune cells, which accumulate with age, need to be investigated. Further comprehensive genetic studies could also help provide insights into the potential contribution of deleterious variation in the severe SARS-CoV-2–associated multisystem inflammatory syndrome in children (*15*). Although the studies of Zhang *et al.* and Bastard *et al.* illuminate the importance of pathways responsible for clearing infections, it is also possible that proinflammatory variants may either reduce or enhance disease severity. Why some patients who carry pathogenic variants in innate immune genes, such as IFN-related genes, remain asymptomatic until their exposure to a specific pathogen is likely explained by the presence of other genetic modifying alleles or epigenetic factors. Unbiased genomic studies can answer some of these questions; however, they need to be expanded to larger and more diverse populations (beyond mostly European descent) to meaningfully address the susceptibility to SARS-CoV-2 and other potentially pandemic viral infections. Ultimately, through collaborative efforts, biomedical research should and will help combat spread of the virus by identifying people at risk with rapid diagnostic tests and facilitating new targeted therapies. ■

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