EDITORIAL

Molecular Underpinnings of Severe Coronavirus Disease 2019

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The molecular underpinnings of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the disease it causes, coronavirus disease 2019 (COVID-19), are poorly understood. Inherited genetic variation is an important tool to disentangle cause and consequence, which in turn can generate insights to guide therapeutic interventions to prevent or treat disease. To date, little is known about genetic susceptibility to SARS-CoV-2 infection and severe forms of COVID-19.[1,2]

Related article

In this issue of *JAMA*, van der Made and colleagues[3] describe 2 independent families with rare germline variants in an innate immune-sensing gene, toll-like receptor 7 (*TLR7*), that lead to severe disease in males who inherit the mutated gene on a single copy of their X chromosome. The study implicates TLR7 as a critical node in recognizing SARS-CoV-2 and initiating an early immune response to clear the virus and prevent the development of COVID-19.

The innate immune system provides the first line of defense against viruses.[4] Upon infecting cells in the respiratory tract, the single-strand RNA structure of SARS-CoV-2 is recognized by TLR7 within endosomes, which leads to the induction of proinflammatory cytokines and interferons.[5] In most individuals, this immune response is sufficient to clear the virus and prevent the development of severe disease.

In some individuals, however, the immune system does not clear the virus, leading to viral replication and spread. In other individuals, an overactive immune system may control viral replication but result in collateral damage to neighboring tissue. Both scenarios, insufficient control of viral replication or an exuberant immune response, may lead to severe respiratory disease, organ failure, and death.

But this creates a therapeutic paradox: if insufficient control of viral replication is a driver of severe disease, then therapies that boost the immune system (eg, interferons[6]) may be beneficial in clearing SARS-CoV-2, especially early in infection. If an overexuberant immune response is a driver of severe disease, then therapies that dampen the immune response (eg, dexamethasone[7]) may be beneficial, especially later in disease.

The study by van der Made and colleagues[3] implicates insufficient control of viral replication via TLR7 and innate immune sensing as a driver of severe COVID-19 in young, previously healthy males from 2 independent families. In the first family, the index case was a male patient, age 32 years, with severe COVID-19 requiring mechanical ventilation in the intensive care unit (ICU). His 29-year-old brother died of COVID-19. Whole-exome sequencing was performed in the index case, leading to the discovery of a 4-nucleotide hemizygous deletion likely leading to a predicted total loss of function of *TLR7* by introducing a premature termination codon (c.2129_2132del; p.[Gln710Argfs*18]). The same mutation, which was confirmed by Sanger sequencing, was identified in a hemizygous state in the deceased male sibling and in a heterozygous state in the uninfected mother, but not the father, consistent with X-linked inheritance from the maternal lineage. The mutation was not present in any individual from the gnomAD database,[8] indicating that the mutation is extremely rare in the general population. Functional studies using peripheral blood mononuclear cells (PBMCs) from hemizygous carriers of the mutation—*TLR7* mRNA expression and type 1 interferon-related gene expression (*IFNB1*, *IRF7*, and *ISG15*) following imiquimod stimulation—are consistent with the in silico predictions that the mutation is loss of function.

The index case in the second family was a male patient, age 21 years, with severe COVID-19 complicated by pulmonary embolisms requiring mechanical ventilation in the ICU. His 23-year-old brother had severe COVID-19 and required ICU care. Exome sequencing revealed a missense variant (c.2383G>T; p.[Val795Phe]), which was predicted as deleterious in all in silico prediction tools. Sanger sequencing confirmed the mutation in the index case and found that the same mutation was inherited by his affected brother. As in family 1, functional studies using PBMCs from one hemizygous carrier were consistent with the in silico predictions that the *TLR7* mutation leads to loss of function.

The presence of 2 independent, rare mutations in a single gene (*TLR7*) in 2 families with an unusual presentation of COVID-19 (severe disease in young, previously healthy males) is statistically unlikely to have occurred by chance alone. However, without independent replication in additional individuals, other explanations for this observation are formally possible (eg, chance, rare variants in other genes, polygenic inheritance).

What are the diagnostic and therapeutic implications of this genetic study for SARS-CoV-2 and COVID-19? First, the *TLR7* mutations in these 2 families are extremely rare. Based on data from large, population-scale databases,[8] rare mutations in *TLR7* are unlikely to be an explanation for severe COVID-19 in the general population. Furthermore, there is no evidence to date that common variants in *TLR7* increase the risk of severe COVID-19. As large-scale genome-wide association studies (GWAS) and whole-genome sequencing studies are performed in other SARS-CoV-2–infected patients, it will be important to investigate common and rare variants in *TLR7* and other innate immune-sensing genes implicated in other immune-related phenotypes (eg, *IFIH1*, *STING*, *MYD88*, *IRAK4*, and *NLRP3*) as drivers of severe COVID-19.

Second, therapeutic interventions that boost the innate immune response to control viral replication early in infection may be beneficial in preventing severe disease. To date, antiviral or anti-inflammatory therapies that show evidence of clinical benefit early in infection have all been repurposed from infectious diseases and indications other than SARS-CoV-2 and COVID-19. For example, remdesivir, originally developed to treat hepatitis C virus and shown to be effective against Ebola virus, has demonstrated clinical benefit in early COVID-19.[9,10] Interferon beta-1b therapy, developed to treat multiple sclerosis and shown to have antiviral activity, also has suggestive evidence of clinical benefit in early SARS-CoV-2 infection.[6] As more information is learned, it should be possible to specifically design therapies against SARS-CoV-2 (eg, neutralizing antibodies against the spike protein[11]).

Third, therapeutic interventions that dampen the immune response may also be beneficial, but timing relative to infection and administration in those with evidence of a maladaptive immune response will be important. For example, a randomized clinical trial showed that the repurposed anti-inflammatory drug dexamethasone was effective in patients with severe COVID-19 requiring mechanical ventilation.[7] There does not appear to be clinical benefit of dexamethasone in earlier stages of COVID-19, although additional studies are required.

Fourth, additional genetic studies, such as whole-genome sequencing as performed by van der Made and colleagues[3] or GWAS as performed by others,[1,2] may guide repurposing of other therapies in early SARS-CoV-2 infection or later-stage COVID-19 disease.[12] Several approved anti-inflammatory therapies are targeted against the protein products of genes with genetic variants that can be used as "instruments" to probe whether perturbations in function lead to clinical phenotypes in SARS-CoV-2 infection (eg, genes implicated in autoimmune diseases or rare forms of primary immune deficiency).

In conclusion, the study by van der Made and colleagues[3] provides evidence that rare mutations in *TLR7* were associated with severe COVID-19 in young males from 2 independent families. While rare mutations in *TLR7* are unlikely to be a major driver of severe disease in most individuals infected with SARS-CoV-2, the genetic study begins to unravel the molecular underpinnings of COVID-19. As additional genetic loci are identified, such data could lead to improved diagnostics and therapeutics, including rational repurposing of existing anti-inflammatory therapies in either early infection or late-stage severe disease.

ARTICLE INFORMATION

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