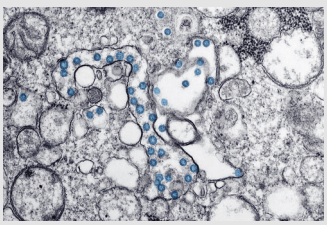
NEWS

HLA variability may help determine COVID-19 disease severity

Westend61/Getty

The highly polymorphic human leukocyte antigen (HLA) genes are critical to the immune system's viral antigen presentation pathway. Research has shown that different HLA alleles can render an individual more susceptible to disease and severe symptoms. Now, in a recent article published in the *Journal of Virology* (https://jvi.asm.org/content/early/2020/04/16/JVI.00510-20.long), Nguyen and colleagues explore how HLA variation may affect vulnerability to COVID-19. The researchers conducted an in silico binding affinity analysis of all possible 8- to 12-mers from the SARS-CoV-2 proteome that are predicted to transit through the MHC class I antigen processing pathway. The analysis revealed that the HLA-B*46:01 allele showed the fewest predicted binding peptides for SARS-CoV-2, suggesting that this allele may make individuals more susceptible to COVID-19. The results are in agreement with a similar analysis the researchers undertook using peptides from the closely related SARS-CoV virus and fits with previous research associating this allele with SARS-CoV disease severity. Next, the group investigated whether prior exposure to common coronaviruses might confer cross-protective immunity. They aligned reference proteome sequence data for five viral proteins from 34 distinct alpha- and betacoronaviruses, including all known human coronaviruses. They found that 564 SARS-CoV-2 8- to 12-mer peptides shared 100% identity with sequences from common human coronaviruses. The scientists then performed binding affinity predictions for these potentially cross-protective peptides across 145 HLA alleles. HLA-B*15:03 was the top presenting allele of the conserved peptides, indicating that it may confer cross-protective immunity. However, more than 50 HLA alleles did not show appreciable binding affinity (<500 nM) to any of the conserved SARS-CoV-2 peptides, suggesting that the potential for cross-protective immunity from other human coronaviruses is low. Finally, the researchers found that differences between HLA alleles with the highest and lowest predicted capacity to present SARS-CoV-2 peptides remained significant at the haplotype level. When they analyzed full HLA genotype data from more than 3000 individuals, they saw wide variability in the ability to present SARS-CoV-2 peptides. Together, the results suggest that individual HLA, haplotype, and genotype variability affect responses to SARS-CoV-2 infection. The authors acknowledge that, as they were unable to obtain data from patients with COVID-19, the work is theoretical. However, they recommend integrating HLA testing into clinical trials and, where practical, combining HLA typing with COVID-19 testing to better predict viral severity in the population and possibly tailor vaccine strategies to genotypically at-risk populations. —*V. L. Dengler, News Editor*

Transcriptomics reveals inflammatory host responses in COVID-19 patients



Hannah A Bullock, Azalbi Tamin

Fever, cough, myalgia, and shortness of breath are characteristic COVID-19 symptoms. Additionally, an immune dysregulation known as hypercytokinemia, or "cytokine storm," has been implicated in severe cases. However, questions remain regarding the host immune response to SARS-CoV-2 infection. As recently reported in *Cell Host & Microbe* (https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30244-4), Zhou and colleagues used metatranscriptomic sequencing to investigate immune signatures in the lungs of eight laboratory-confirmed COVID-19 patients. The researchers sampled patients with bronchoalveolar lavage, a method to recover lung cells and solutes, which enabled them to analyze gene expression profiles from both the host and the virus, and construct an in situ picture of the host response to SARS-CoV-2 infection. Compared with healthy controls, expression levels of proinflammatory cytokine and chemokine genes, antiviral interferon-stimulated genes (ISGs), and calgranulin genes were upregulated in SARS-CoV-2-infected individuals (SARS2). The chemokine gene *CXCL17* saw robust upregulation in the SARS2 group, occurring in all eight COVID-19 cases, but did not reach significant differential expression from individuals with community-acquired pneumonia (CAP). Together, the results suggest that *CXCL17* may be involved in COVID-19 pathogenesis. The researchers then assessed chemokine gene expression changes in each COVID-19 case. They found that one individual with marked chemokine upregulation also displayed ultrahigh viral reads, indicating that higher virus replication led to a stronger proinflammatory response. When the researchers lined up individual cases according to the number of days between sampling and symptom onset, they found that, with the exception of a patient who succumbed to the disease, expression levels of cytokine-related genes tended to decrease over time. The finding suggests that abundant inflammation could resolve, but that unrestrained inflammation may lead to poor outcomes. Similarly, expression levels of ISGs were notably higher in SARS2 than CAPs, and decreased over time, except in the fatal case. More than a third of upregulated ISGs in SARS2 are involved in inflammation regulation, pointing to an immunopathological role of IFN response in COVID-19 patients. Finally, the investigators examined the composition of cells from the bronchoalveolar lavage fluid. Whereas healthy individuals mainly harbored macrophages and lymphocytes, neutrophils were the predominant cells from SARS2 patients, resulting in a high neutrophil-to-lymphocyte ratio, which has been linked to COVID-19 disease severity. The authors conclude that the collective results further our understanding of COVID-19 pathogenesis and facilitate antiviral strategies. —*V. L. Dengler, News Editor*

Genetics in Medicine (2020) https://doi.org/10.1038/s41436-020-0860-z