Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

One of the most perplexing features of coronavirus disease 2019 (COVID-19) is the fact that the disease can range from silent infection to lethal outcome in different individuals. In the current study, Zhang et al (Science 2020;370(6515):eabd4570; PMID: 32972995) demonstrate an enrichment in rare variants predicted to be loss-of-function (LOF) at 13 human loci known to govern Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (IRF7)-dependent type I interferon (IFN) immunity to influenza virus. The IFN-I family includes IFN-α, IFN-β and IFN-ω. These molecules provide innate immune defenses. The authors sequence the exome or genome from 659 patients with life-threatening COVID-19 pneumonia, relative to subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, the authors define LOF variants underlying autosomal-recessive or autosomal-dominant deficiencies in 23 patients (3.5%) carrying 24 deleterious variants of eight genes. The authors demonstrate that human fibroblasts with mutations affecting this circuit are vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The authors conclude that inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

In the current study, Bastard et al (Science 2020; doi: 10.1126/science.abc4585; PMID: 32972996) tested the interindividual variability in coronavirus disease 2019 (COVID-19). The authors demonstrate that at least 101 of 987 patients with life-threatening pneumonia had neutralizing immunoglobulin G (IgG) autoantibodies (auto-Abs) against interferon-ω (IFN-ω) (13 patients), against the 13 types of IFN-α (36), or against both (52) at the onset of critical disease. The auto-Abs neutralize the ability of the corresponding type I IFNs to block the viral infection in vitro. Furthermore, the auto-Abs were not found in 663 individuals with asymptomatic or mild infection and were present in only 4 of 1227 healthy individuals. The authors conclude that the neutralizing auto-Abs against type I IFNs, like inborn errors of type I IFN production (shown in the accompanying study above), tip the balance in favor of the virus, which results in devastating disease with insufficient innate and adaptive immune responses.

Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein

In the current study, Toelzer et al (Science 2020; doi: 10.1126/scitranslmed.abd3876; PMID: 33139519) investigate the cryo-electron microscopic (cryo-EM) structure of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) to determine the mechanisms driving high infectivity and broad tissue tropism of the virus. The authors evaluate the 2.85 Å cryo-EM structure of SARS-CoV-2 spike (S) glycoprotein and demonstrate that the receptor binding domains (RBDs) tightly bind the essential free fatty acid (FFA) linoleic acid (LA) in three composite binding pockets. The pocket also appears to be present in the highly pathogenic coronaviruses SARS-CoV and MERS-CoV. Furthermore, binding by LA stabilizes a locked S conformation, leading to reduced interaction with angiotensin converting enzyme 2 (ACE2). In human cells, LA supplementation synergizes with the COVID-19 drug remdesivir, suppressing SARS-CoV-2 replication. The authors conclude that interaction between LA and S protein is critical to viral infection and may set the stage for intervention strategies targeting LA binding by SARS-CoV-2.

Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19

In the current study, Zuo et al (Sci Transl Med 2020; doi: 10.1126/scitranslmed.abb8386; PMID: 33139519) investigate antiphospholipid syndrome in coronavirus disease 2019 (COVID-19). The authors quantified eight types of autoantibodies targeting phospholipids and phospholipid-binding proteins (aPL antibodies) in serum samples from 172 patients hospitalized with COVID-19. The investigators detected anti-phosphatidylserine/prothrombin (aPS/PT) IgG in 24% of serum samples, anticardiolipin IgM in 23% of samples, and aPS/PT IgM in 18% of samples. Higher titers of aPL antibodies were associated with neutrophil hyperactivity including the release of neutrophil extracellular traps, higher platelet counts, more severe respiratory disease, and lower clinical estimated glomerular filtration rate. The authors conclude that at least half of patients hospitalized with COVID-19 become transiently positive for aPL antibodies and that these autoantibodies are potentially pathogenic.