Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses — are we our own worst enemy?

Lok-Yin Roy Wong and Stanley Perlman

Abstract | Human coronaviruses cause a wide spectrum of disease, ranging from mild common colds to acute respiratory distress syndrome and death. Three highly pathogenic human coronaviruses — severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus and SARS-CoV-2 — have illustrated the epidemic and pandemic potential of human coronaviruses, and a better understanding of their disease-causing mechanisms is urgently needed for the rational design of therapeutics. Analyses of patients have revealed marked dysregulation of the immune system in severe cases of human coronavirus infection, and there is ample evidence that aberrant immune responses to human coronaviruses are typified by impaired induction of interferons, exuberant inflammatory responses and delayed adaptive immune responses. In addition, various viral proteins have been shown to impair interferon induction and signalling and to induce inflammasome activation. This suggests that severe disease associated with human coronaviruses is mediated by both dysregulated host immune responses and active viral interference. Here we discuss our current understanding of the mechanisms involved in each of these scenarios.

Coronaviruses can cause highly pathogenic diseases in humans, as evidenced by three major outbreaks within the past two decades. The severe acute respiratory syndrome (SARS) epidemic first occurred in 2002 and was later eradicated, but caused around 8,000 cases of disease, with mortality of roughly 10%1. The Middle East respiratory syndrome (MERS) epidemic is still ongoing, predominantly in the Middle East, with more than 2,000 cases and 800 deaths occurring since MERS coronavirus (MERS-CoV) was first identified in 2012 (REF2). The current COVID-19 pandemic, caused by SARS coronavirus 2 (SARS-CoV-2), has resulted in more than 242 million cases, with a death toll of more than 4.9 million people (as of 25 October 2021 (REF3)). In light of the continuous efforts to understand these highly pathogenic coronaviruses, scientists have described the immunopathological nature of immune responses to these coronaviruses. Highlighting this, host immune dysregulation has been shown to contribute to disease severity and to determine disease outcome in these infections. However, abundant evidence has also demonstrated that active immune evasion by viral proteins encoded by SARS-CoV, MERS-CoV and SARS-CoV-2 further contributes to the dysregulation of host immune processes. In this Perspective, we summarize current knowledge of host immune dysregulation during infection with SARS-CoV-2 and related human coronaviruses. We also describe and discuss the immunopathological host response and the mechanistic role of viral proteins in the active manipulation of the host immune system.

Dysregulated interferon responses

Conflicting data on the role of interferons in coronavirus infection. Interferons are a group of antiviral cytokines that are induced during viral infections. The antiviral functions of interferons can be largely attributed to interferon-stimulated genes (ISGs). ISGs are upregulated by interferons during viral infection to perform critical effector functions for virus containment and clearance. Antiviral effector functions of ISGs include, but are not limited to, inhibiting virus entry, replication, translation and egress4. In addition to direct antiviral functions, ISGs also regulate adaptive immune responses by recruiting and directing the differentiation of immune cells4. The protective roles of the interferon pathway have been evidenced by studies reporting that patients with COVID-19 who have genetic defects in interferon signalling pathways or have autoantibodies to interferon have poor disease outcomes. Ten per cent of patients with life-threatening COVID-19 had serum autoantibodies to type I interferon, while 3.5% of patients with severe COVID-19 had genetic defects at loci involved in Toll-like receptor 3 (TLR3)-dependent and interferon-regulatory factor 7 (IRF7)-dependent expression and amplification of type I interferon5-7. In this regard, the benefits of interferon in combination with other antiviral molecules as therapeutic treatments for coronavirus infection have been tested in clinical trials. However, these studies have shown inconsistent results, probably reflected by the timing of interferon administration and thus highlighting the limitations of the direct use of interferons as therapeutic options5-11. The conventional idea that the interferon response is protective in coronavirus infection has been challenged by some studies that suggest pathological roles of the interferon response, especially at the peak of virus replication. For example, this understanding of the role of the interferon response has been complicated by the different clinical outcomes observed in patients. In a clinical study of 40 patients with SARS, robust early interferon and ISG expression were hallmarks of severe disease12. Most patients in the study resolved the interferon response as part of disease resolution and their production of antibodies to SARS-CoV rose, leading to better outcomes. However, patients with a persistent interferon response showed lower oxygen saturation levels, lower levels of antibodies to SARS-CoV and poor
clinical outcomes. This study suggests that persistent interferon responses precluded the switch from innate to adaptive immunity as SARS progressed, resulting in severe disease in some patients. In a longitudinal study of clinical samples from patients with COVID-19, elevated interferon expression was detected in the blood only of patients with severe disease, and elevated levels of interferons correlated with disease severity and mortality, in support of a pathological role of interferon. However, in other studies, early interferon responses were observed and found to later resolve in patients with mild-to-moderate COVID-19, whereas upregulation of interferon was not seen in patients with severe disease. It is not surprising to observe different temporal expression patterns of interferon in relation to disease severity in these different studies, as clinical samples were collected from patients with variable demographic profiles and at different times relative to disease progression, complicating the analysis and interpretation in clinical settings.

Contrasting results have also been obtained in studies of the role of interferon signalling in SARS-CoV-infected mice. Serial passaging of human isolates of SARS-CoV in BALB/c mice resulted in the emergence of six mutations throughout SARS-CoV in BALB/c mice infected with a lethal dose of MERS-MA15 owing to impaired type I interferon signalling downstream of IFNAR, resulting in delayed and sustained upregulation of interferon responses for extended periods and without resolution in comparison with wild-to-moderate cases. These results corroborate findings in murine models of SARS and MERS. Virus titres in the lungs of BALB/c mice infected with SARS-MA15 peaked before the peak of interferon expression, and the detrimental effects of interferon signalling in BALB/c mice were attributed to this delay in interferon expression relative to the peak of virus titres. This was supported by the protective role of interferon treatment provided before the peak of virus replication, but not when interferon was provided after the peak of virus replication. The therapeutic role of interferon in MERS was also tested in a murine model where exons 11–14 of the gene encoding human dipeptidyl peptidase 4 (hDPP4), the receptor for MERS-CoV, were knocked in to C57BL/6 mice (hDPP4-KI mice). Similarly to the SARS study, early interferon treatment of MERS-CoV-infected mice converted an otherwise uniformly lethal infection to a sublethal infection, while delaying interferon treatment until after the peak of virus replication exacerbated disease and resulted in significantly higher mortality. In SARS-CoV-2 experimentally infected animal models, treatment with interferon or interferon receptor agonists before infection offered protection against severe disease. In addition, hamsters challenged with SARS-CoV-2 were protected by prophylactic interferon treatment (1 day before infection) or early interferon treatment (1 day after infection), while late interferon treatment (3 days after infection) conferred no protection. Thus, the apparently contradictory results of exogenous interferon treatment in different mouse strains could potentially be explained by different replication kinetics of the virus between these mouse strains. In support of this, endogenous interferon signalling was protective in mice infected with a mouse-adapted version of MERS-CoV (MERS-MA30) but was pathogenic in SARS-MA15-infected mice. SARS-MA15 replicated to peak titres at 16 hours after infection in BALB/c mice, whereas titres of MERS-MA30 peaked at 2 days after infection in hDPP4-KI mice. It was therefore proposed that the timing of interferon production relative to the peak virus titres, which is specific to the host and virus in context, dictates the nature of host endogenous interferon signalling and the outcome of exogenous interferon treatment.

Several studies have attempted to delineate the pathological roles of interferon signalling in mice infected with human coronaviruses. Pathological consequences of endogenous or exogenous type I interferon were shown to be mediated in part by the infiltration of inflammatory monocytes and macrophages into the lungs of infected mice. In hDPP4-KI mice infected with a sublethal or lethal dose of MERS-MA30, mice that received interferon exogenously at early times after infection had significantly fewer activated monocytes and macrophages in their lungs than infected mice that were not treated with interferon. Moreover, the severe disease observed in SARS-MA15-infected BALB/c mice or in mice that received interferon coincident with peak virus titres was associated with notably higher numbers of activated monocytes and macrophages in the lungs. The detrimental effects of enhanced inflammatory monocyte infiltration were nullified by treatment with a monocyte-depleting anti-CCR2 antibody, confirming the key role of these cells in exacerbating disease. In addition,
human autopsy studies and analyses of peripheral blood mononuclear cells also identified elevated numbers of monocytes and macrophages in the lungs and blood of patients with severe COVID-19 (Ref 27–29). Transcriptomic analyses revealed a robust interferon gene signature in macrophages from the airways of patients with COVID-19, supporting the idea that monocytes and macrophages mediate the immunopathological effects of interferon. For example, interferon signalling resulted in the upregulation of pro-inflammatory cytokines in macrophages in these studies, possibly contributing to immunopathological changes (Ref 30–33).

Additional studies in mice showed that type I interferon/type III interferon inhibition regulated the lung epithelia, in part by inducing the expression of the tumour suppressor protein p53, which impaired the proliferation of alveolar type II cells and differentiation of basal cells during recovery (Ref 34,35). Consistent with these observations, treatment of mice with poly(I-C), a Toll-like receptor 3 (TLR3) agonist, resulted in inhibition of lung epithelial repair (Ref 36). Together, these results suggest that elevated expression of type I and type III interferons in the lower airways of patients with severe COVID-19 during the late acute period, after virus titres have peaked, contributes to poor outcomes through interferon-mediated inhibition of lung epithelial regeneration (Ref 37). These results indicate that a temporally dysregulated type I interferon/type III interferon response can impair all parts of the host response to infection. They also suggest that localized effects of interferon signalling need to be considered as the role of interferon in COVID-19 is further investigated (Ref 38).

**Interferon antagonism by viral proteins encoded by coronaviruses.** In addition to the host factors that contribute to a dysregulated interferon response, coronaviruses exhibit variable sensitivity to interferon, and SARS-CoV, MERS-CoV and SARS-CoV-2 all encode interferon antagonists that actively interfere with host interferon induction and/or signalling (Ref 39–44). In particular, MERS-CoV and SARS-CoV-2 are more sensitive to interferon than SARS-CoV, and these two viruses inhibit interferon induction to a greater extent than SARS-CoV. However, SARS-CoV and SARS-CoV-2 appear to inhibit IFNAR signalling to a greater extent than MERS-CoV (Ref 37,38).

Viral proteins encoded by coronaviruses can be broadly classified into three groups: structural proteins, non-structural proteins and accessory proteins (Fig. 1). Each group of proteins is responsible for specific functions of the viral life cycle. For example, non-structural proteins are critical for viral RNA transcription and replication by forming the replication–transcription complex. Structural proteins include the spike (S), envelope (E), membrane (M) and nucleoprotein (N) proteins, which are essential for the formation of virions. Accessory proteins are dispensable for the viral life cycle but are important for immunoevasive activities. With the goal of identifying interferon antagonists encoded by SARS-CoV-2, in vitro screening using singly transfected SARS-CoV-2 viral proteins was performed. The results suggested that non-structural protein 1 (nsp1), nsp3, nsp12, nsp13, nsp14, nsp15, nsp16, open reading frame 3 (ORF3) protein, ORF6 protein, M protein and N protein are interferon antagonists that suppress interferon expression in various stimulation conditions that mimic SARS-CoV-2 infection (Ref 41–43) (Fig. 2).

Conserved interferon-antagonizing functions among viral proteins encoded by coronaviruses highlight the important role of interferon antagonism in coronavirus evolution. As an example of this, SARS-CoV ORF6 protein was shown to inhibit interferon signalling by binding karyopherin subunit-a2 (Ref 44), which impeded STAT1 nuclear translocation. In the case of SARS-CoV-2, ORF6 protein hijacks the nuclear pore complex to block STAT1 nuclear translocation (Ref 45), while ORF9b protein interacts with mitochondrial import receptor subunit TOM70 to suppress interferon expression (Ref 46). In another example, nsp16 is a 2′-O-methyltransferase found in all coronaviruses that inhibits the recognition of viral RNA by intracellular helicases (Ref 47). nsp16 functions by methylating the 2′-hydroxy group of the first base to form a cap 1 structure to mimic cellular mRNA. In addition, the N protein was shown to undergo liquid–liquid phase separation with RNA to impede interferon expression by preventing MAVS aggregation (Ref 48). One caveat regarding the screening of interferon antagonists is that most studies thus far have used tissue culture cells with ectopic expression of the protein of interest. In many of these assays, viral proteins were expressed singly in the absence of other viral proteins and often at supraphysiological levels. Results obtained from these experiments should be interpreted with caution, and these results need to be verified using recombinant viruses genetically depleted of the protein of interest. For some proteins, such as the M and N proteins, this is not feasible since they are essential for virus growth. In these cases, it may be possible to perform mutational analyses...
to identify specific amino acids important for immune evasion but not virus viability. Another key issue that should be addressed is that blood type I interferon levels are low in patients with severe COVID-19, even though these anti-interferon effects would be expected primarily to inhibit interferon production by infected cells and not bystander cells.

**Increase in pro-inflammatory mediators**

The initial innate inflammatory response to coronaviruses facilitates the rapid recruitment of immune cells to the main site of infection (the lungs) and the subsequent activation, differentiation and proliferation of these cells. Despite enabling pathogen clearance, this immune response may result in immunopathological changes if unchecked. Multiple reports have indicated pathologically heightened inflammatory responses in patients infected with SARS-CoV, MERS-CoV or SARS-CoV-2 and in animal models of these infections. This was demonstrated by the detection of elevated levels of cytokines and chemokines — including IL-1β, IL-6, IL-8 and tumour necrosis factor (TNF) — in the blood during

**Fig. 2 | Antagonism of interferon signalling by SARS-CoV-2 and related coronaviruses.** Coronavirus RNA in the cytoplasm is sensed by the cytoplasmic RNA sensors RIG-I and MDA5. Sensing of viral RNA triggers conformational changes in these sensors and results in the recruitment of downstream effector proteins. MAVS interacts with RIG-I or MDA5 through CARD domains to recruit the downstream kinases TBK1 and IKKε for phosphorylation of interferon-regulatory factor 3 (IRF3) and IRF7. MAVS activation also recruits TNF receptor-associated factor 6 (TRAF6), which serves as an adapter for the IKK complex (NEMO, IKKα and IKKβ). The IKK complex phosphorylates NF-κB canonical inhibitor, IκB, which results in IκB degradation and activation of NF-κB. IRF3, IRF7 and NF-κB translocate to the nucleus and interact with the corresponding positive regulatory domain (PRD). IRF3 and IRF7 bind PRD I/PRD III, NF-κB binds PRD II, and AP-1 (a heterodimer of JUN and ATF2) binds PRD IV on the interferon-β (IFNβ) promoter to form the interferon enhancersome for induction of IFNβ expression. IFNβ is secreted and interacts with the IFNα/β receptor (IFNAR; comprising the IFNAR1 and IFNAR2 subunits) in an autocrine or a paracrine manner. Binding of interferon to IFNAR activates the signal transducer and activator of transcription 1 (STAT1) and STAT2 kinases, Janus kinase 1 (JAK1) and the tyrosine kinase TYK2. Phosphorylated STAT1 and STAT2 associate with IRF9 to form ISGF3, which translocates to the nucleus and interacts with the interferon-stimulated response element (ISRE) promoter to drive the expression of downstream interferon-stimulated genes (ISGs). ISGs perform different antiviral functions. The example depicted in the figure is the 2′-5′-oligoadenylate synthetase (OAS)–RNase L pathway. OAS interacts with viral RNA and catalyses the formation of 2′-5′-oligoadenylate (2-5A) from ATP. 2-5A is a secondary messenger that activates RNase L to drive viral RNA degradation. Viral proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and related coronaviruses shown in the figure interfere with interferon production and signalling at different steps. Viral proteins (depicted in red) are from SARS-CoV-2 unless otherwise specified. MERS-CoV, Middle East respiratory syndrome coronavirus; N, nucleocapsid protein; nsp, non-structural protein; ORF, open reading frame protein.
infection, and the presence of immune cells in the lungs of deceased patients. High levels of these inflammatory mediators are also correlated with disease severity.

**Dysregulated inflammatory response alters immune landscape.** The precise mechanisms of immunopathology in COVID-19 remain elusive. Sustained IL-6 and TNF production in patients infected with SARS-CoV-2 correlates with reduced monocyte maturation. As a result, MHC class II antigen (HLA-DR) expression on circulating monocytes was reduced, resulting in cells less able to present antigen. In addition, these changes in monocyte maturation are accompanied by depletion of natural killer cells, CD4+ T cells and B cells. HLA-DR expression on monocytes and total lymphocyte counts were partially restored with tocilizumab (a monoclonal antibody to IL-6 receptor) treatment, suggesting a role of sustained IL-6 production in altering the immune landscape.

In addition, multisystem inflammatory syndrome in both child and adult patients with a history of COVID-19 was characterized by elevated blood levels of IL-1β, IL-6, IL-8 and IL-10 (REFS 54–56), suggesting a role for the inflammatory response in pathogenesis. Multisystem inflammatory syndrome in children and adults has cardiac, renal, respiratory, haematological, gastrointestinal, dermatological and neurological manifestations, and fever, neutrophilia, lymphopenia and elevated levels of C-reactive protein, fibrinogen, ferritin, IL-6 and D dimer have been detected in laboratory tests. Animal studies have also indicated a role of elevated levels of inflammatory cytokines in mediating immunopathology in coronavirus infections.

**Coronavirus-encoded viral proteins activate inflammasomes and NF-κB signalling.** NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasomes are activated in SARS-CoV-2-infected human monocytes and in patients with COVID-19 (REFS 54–56). NLRP3 activation results in caspase 1 activation and cleavage of IL-1β and IL-18 into their active forms as well as the initiation of pyroptosis, a highly inflammatory form of cell death. Several SARS-CoV proteins can activate the NLRP3 inflammasome. The SARS-CoV E protein was shown to possess calcium ion channel activity that activates NLRP3 (REF 57). ORF3a protein of SARS-CoV was demonstrated to cause NLRP3 maturation by enhancing ubiquitination of the NLRP3 adaptor protein ASC by TNF receptor-associated factor 3 (TRAF3)39. ORF8 protein of SARS-CoV also activated NLRP3 through direct interaction40. On the basis of their similarity to SARS-CoV proteins, analogous SARS-CoV-2 proteins are also likely to activate NLRP3 in these ways. SARS-CoV infection activated NF-κB signalling, and a hallmark of severe COVID-19 is upregulation of NF-κB-dependent inflammatory molecules, such as IL-1, IL-6, IL-8 and TNF (REF 58). In addition to its role in inflammasome activation, the E protein of SARS-CoV induced NF-κB activation41. Despite clear evidence that inflammasome-dependent and NF-κB-dependent cytokines and chemokines induced by SARS-CoV-2 are critical for COVID-19 immunopathogenesis, not much is known about the viral components responsible for such activation. ORF3a, ORF7a, M and N proteins have been reported to induce inflammatory cytokine expression by activating NF-κB in tissue cultures. However, further analysis is warranted to verify how SARS-CoV-2 induces these inflammatory changes with authentic virus through reverse genetics.

**Complement-mediated immunopathology in coronavirus infections.** The complement system is critical for efficient recognition and elimination of pathogens. However, similarly to the interferon and inflammatory responses, unchecked activation of the complement system can contribute to severe disease. Complement is considered a major component in the endothelitis and thrombosis observed in COVID-19 (REF 59). Complement activation by a coronavirus was first evident in mice infected with SARS-CoV. Deposition of complement activation products was observed in the lungs of C57BL/6J mice as early as 1 day after infection. C57BL/6J mice genetically deficient in C3 complement protein, fibrinogen, ferritin, IL-6 and D dimer have been detected in laboratory tests. Animal studies have also indicated a role of elevated levels of inflammatory cytokines in mediating immunopathology in coronavirus infections.

**Adaptive immunity to coronaviruses.** Adaptive immunity is critical for virus clearance and is dysregulated in patients with severe COVID-19. Coronavirus-specific CD4+ T cells, CD8+ T cells, B cells and antibodies have been identified in patients during acute disease and convalescence and were shown to be protective and required for virus clearance in murine models of SARS, MERS and COVID-19 (REFS 60–62). In mouse models of SARS-CoV, immunization of naive mice with dendritic cells (DCs) pulsed with immunodominant SARS-CoV peptides protected mice from subsequent lethal challenge. In addition, depletion of CD4+ T cells resulted in reduced immune cell recruitment to the lungs and lower levels of neutralizing antibody production, which coincided with enhanced disease. Similar results were seen in mice infected with MERS-CoV or SARS-CoV-2 (REFS 63–65). In patients with COVID-19, virus-specific T cells respond to stimulation with several peptides across the viral genome, while SARS-CoV-2-specific
Coronaviruses

by increased expression of a phospholipase (PLA2G2D) in rDCs in an age-dependent manner. In aged mice, where lung DC migration and subsequent T cell activation were diminished owing to elevated levels of an eicosanoid, prostaglandin D2 (PGD2), and its upstream phospholipase, PLA2G2D, relative to young mice. In aged mice, PGD2 acted on its receptor, PGD2 receptor 1 (DP1), on CD11c+ DCs and suppressed DC migration to the draining lymph nodes, resulting in diminished T cell activation and poor disease outcome relative to young mice. Specifically blocking DP1 signalling on CD11c+ DCs resulted in enhanced DC migration from the lungs to the draining lymph nodes and improved antiviral T cell responses, which partially protected mice from lethal infection with SARS-CoV-2.

Similar results have also been shown for SARS-CoV-2. These results align well with clinical data indicating that advanced age is a risk factor for SARS, MERS and COVID-19.

In addition to studies of experimentally infected animals, evidence indicating the protective role of cellular immune responses in COVID-19 has been described in reports characterizing and comparing T cell responses in asymptomatic, mildly symptomatic and severely symptomatic individuals during acute infection and convalescence. Le Bert et al. compared T cell responses in asymptomatic and symptomatic patients with COVID-19 and identified more robust expression of the T cell effector molecules IL-2 and IFNγ in asymptomatic patients. Longitudinal studies revealed that early induction, emergence of functional SARS-CoV-2-specific T cells targeting diverse epitopes and prolonged contraction of T cell responses are characteristics observed in patients with mild diseases.

Tissue-resident T cells in the airways of patients with COVID-19 exhibit functionally protective phenotypes, with the frequency of these cells correlating with younger age and a higher survival rate. Also, the presence of SARS-CoV-2-specific memory CD4+ T cells and CD8+ T cells in convalescent patients correlated with mild disease. SARS-CoV-2-specific T cells were present in individuals who were in close contact with patients with COVID-19. These individuals were asymptomatic and had no evidence of infection as they tested negative for SARS-CoV-2 by quantitative reverse transcription–PCR testing and did...
not seroconvert\textsuperscript{105,106}. This is an intriguing observation as it is unclear how individuals without confirmed infection developed SARS-CoV-2-specific T cell responses. It is possible that these individuals were transiently infected with SARS-CoV-2, rapidly cleared the infection and still developed a T cell response. However, the current evidence does not preclude the possibility that these individuals were never infected with SARS-CoV-2 and that these SARS-CoV-2-specific T cells were pre-existing common cold coronavirus-specific T cells. Further studies are warranted to characterize the SARS-CoV-2-specific T cells present in these individuals.

**Pathogenic roles of T cells in coronavirus infections.** Despite several lines of evidence suggesting a protective role of the T cell response in coronavirus infections, T cell-mediated pathogenesis has also been reported. This is most notable in mice infected with a murine coronavirus, mouse hepatitis virus (MHV). Infection of susceptible A/J and C3H/HeJ mice with a pneumotropic strain of MHV (MHV-1) resulted in significant pulmonary pathology. Antibody-mediated depletion of CD4\(^+\) T cells and CD8\(^+\) T cells decreased pathological changes in the lungs, suggesting that CD4\(^+\) T cells and CD8\(^+\) T cells induced pulmonary pathogenesis in these mice\textsuperscript{104}. In another example, infection of the central nervous system with the neurotropic JHM strain of MHV (MHV-JHM) induced encephalitis with both acute and chronic demyelination of the central nervous system during T cell-mediated virus clearance\textsuperscript{105–108}. A novel host-resident population of CD4\(^+\)CD8\(^+\) inflammatory monocytes with abundant IL-6 expression that potentially led to a hyperinflammatory state in patients was never infected with SARS-CoV-2 and that these SARS-CoV-2-specific T cells were pre-existing common cold coronavirus-specific T cells. Further studies are warranted to characterize the SARS-CoV-2-specific T cells present in these individuals.

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mutations in the S protein that enhance transmission and make this variant more resistant to neutralization by convalescent plasma and vaccine-induced sera126,127,128. In particular, the E484K mutation found in the S protein of B.1.351 is the major driver in neutralizing antibody resistance. L452R and N501Y mutations in the S protein have been shown to result in enhanced binding of SARS-CoV-2 to its entry receptor on human cells, ACE2 (REFS 23,24). The emergence of SARS-CoV-2 variants with increased resistance to antibody neutralization is alarming. However, correlates of protection have not been well defined, and some vaccines induce an antibody response that remains protective upon exposure to variant viruses129. Of note, the duration of immunity to original strains or variants remains unknown. It is therefore important to achieve high levels of neutralizing antibodies through vaccination to maximize the protective margin against these variants. Also, active somatic hypermutation for antibody maturation over time could enhance antibody neutralization, which could potentially offer sufficient protection against these variants.21

Potential pathogenic role of antibody response in coronavirus infection. Antibody-dependent enhancement is one of the most concerning outcomes of infection or reinfection with SARS-CoV-2 after vaccination or natural infection. However, in the case of coronaviruses, antibody-dependent enhancement, or enhanced infection of macrophages, has been observed only in felines infected with feline infectious peritonitis virus. Macrophages are productively infected with feline infectious peritonitis virus, and infection is enhanced by treatment with sera from infected cats or by vaccination with S protein-containing constructs21,22. Classical antibody-dependent enhancement requires interaction between virus–antibody immune complexes and Fc receptors on macrophages to enhance infection23. In SARS-CoV-2, macrophages are only abortively infected despite induction of an inflammatory response in these cells124,129; thus, classical antibody-dependent enhancement is unlikely to occur in SARS-CoV-2 infection130. In addition, in the case of SARS-CoV infection, anti-S protein antibodies have been shown to change the phenotype of lung-infiltrating macrophages from wound healing to pro-inflammatory, although this did not affect clinical disease observed after challenge131.

Another factor in antibody protection versus pathogenicity is related to Fc effector function. For example, afucosylation of the Fc region of antibodies enhances their activity by increasing Fc engagement with Fcγ receptor IIa and Fcγ receptor III (REF. 132). This may result in increased protective efficacy but may also result in enhanced macrophage activation and aberrant induction of inflammatory cytokines (such as IL-6 and TNF) that are key for COVID-19 pathogenesis133,134. Macrophages that are robustly activated by afucosylated antibodies may damage pulmonary endothelial walls and induce thrombosis in the microvasculature135. High levels of afucosylated SARS-CoV-2 antibodies have been found in patients with severe COVID-19 (REFS 135–138). These results illustrate the importance of appropriate Fc modifications to prevent immunopathology mediated by antibody response.

Concluding remarks

In this Perspective, we have provided an overview of the current knowledge of innate and adaptive immune dysregulation mediated by the host (immunopathogenic) and the virus (active interference by virus). COVID-19 serves as an excellent example of the complexity and interdependent nature of host immune homeostasis. Once disrupted, as in the case of COVID-19, the consequences are a series of immunopathological changes that lead to disease progression. A more comprehensive understanding of these changes could allow us to develop more effective therapies for the treatment of patients who develop severe disease as a consequence of coronavirus infection.

Lok-Yin Roy Wong 1 and Stanley Perlman 1,2 21st
1Department of Microbiology and Immunology, University of Iowa, Iowa City, IA, USA.
2Department of Paediatrics, University of Iowa, Iowa City, IA, USA.
✉ e-mail: stanley-perlman@uiowa.edu
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