

PERSPECTIVE

Immune asynchrony in COVID-19 pathogenesis and potential immunotherapies

Ting Zhou^{1*}, Tina Tianjiao Su^{1*}, Tenny Mudianto², and Jun Wang^{2,3}

The outbreak of coronavirus disease 2019 (COVID-19) is an unprecedented global health crisis. Tissue and peripheral blood analysis indicate profound, aberrant myeloid cell activation, cytokine storm, and lymphopenia, with unknown immunopathological mechanisms. Spatiotemporal control of the quality and quantity of the antiviral immune responses involves synchronized cellular and molecular cascades and cross-talk between innate and adaptive immunity. Dysregulated responses in immunity, such as at the stages of immune sensing, alarming, polarization, and resolution, may contribute to disease pathology. Herein, we approach SARS-CoV-2 through an immunomodulatory lens, discussing possible mechanisms of the asynchronized antiviral immune response and proposing potential therapeutic strategies to correct the dysregulation.

Introduction

The recurring outbreaks of viruses within the Coronaviridae family, such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and now SARS-CoV-2, demonstrate the grave threat that these viruses pose to humanity. SARS-CoV-2 is considered less lethal than SARS-CoV and MERS-CoV but more contagious (Perlman and Netland, 2009; Sanche et al., 2020). Despite some knowledge regarding the epidemiology and clinical presentation of the resulting disease, COVID-19, much less is understood regarding its pathobiology (Guan et al., 2020).

Angiotensin-converting enzyme 2 (ACE2) has been identified as the major SARS-CoV-2 receptor critical for the infection of lung epithelial cells and other tissues (Hoffmann et al., 2020; Zhou et al., 2020a). However, viral load from the nasopharynx does not appear to be a good biomarker correlating with disease severity and mortality; indeed, patients with severe disease can present with low viral titers, while high viral titers have been observed in asymptomatic individuals (Lescure et al., 2020; Zou et al., 2020). SARS-CoV-2 and its family members share some puzzling, unique pathological features, most notably acute respiratory distress syndrome (ARDS), cytokine release syndrome (CRS), and lymphopenia, despite excessive myeloid cell-dominant inflammation, which has been correlated with COVID-19 severity (Vabret et al., 2020). Moreover, single-cell RNA sequencing studies on the nasopharyngeal and bronchial samples from COVID-19 patients revealed the existence of the viral genome in immune cells (Bost et al., 2020; Chua et al., 2020).

These findings highlight possible direct viral-immune engagement and an essential, pathogenic signature of immune dysregulation. Here, we present a model of intermolecular and intercellular immune asynchrony, based on dysregulation of timing, localization, quality, and quantity of the immune response, to explain the immunopathogenesis of COVID-19. We also propose potential strategies to correct the viral-induced immune dysregulation.

Antiviral immunity: A multifactorial but synchronized system

The activation, recruitment, and resolution of an antiviral immune response is composed of efficiently organized cellular and molecular cascades that tightly regulate the balance between viral clearance and immune toxicity (Fig. 1). Upon virus infection, multiple innate immune recognition mechanisms can detect the virus, recognizing pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs; Vabret et al., 2020), or viral proteins (Koch et al., 2013). Within hours, the sensing apparatus triggers a rapid antiviral response to inhibit viral replication, primarily through type I/III IFN production (Stetson and Medzhitov, 2006), together with other cytokines (e.g., IL-1, IL-18, and IL-6) and chemokines (e.g., CCL2 and CCL7). Over the course of several days, adaptive immunity is activated and subsequently down-regulates innate immunity to avoid nonspecific damage to the host (Kim et al., 2007). As the pathogen is eliminated, various innate (e.g., M2 macrophages and regulatory dendritic cells) and adaptive regulatory cell types (e.g., regulatory T and B cells) also help resolve

¹Department of Immunobiology, Yale University School of Medicine, New Haven, CT; ²Department of Pathology, New York University Grossman School of Medicine, New York, NY; ³The Laura and Isaac Perlmutter Cancer Center, New York University Langone Health, New York, NY.

*T. Zhou and T.T. Su contributed equally to this paper; Correspondence to Jun Wang: jun.wang@nyulangone.org.

© 2020 Zhou et al. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).

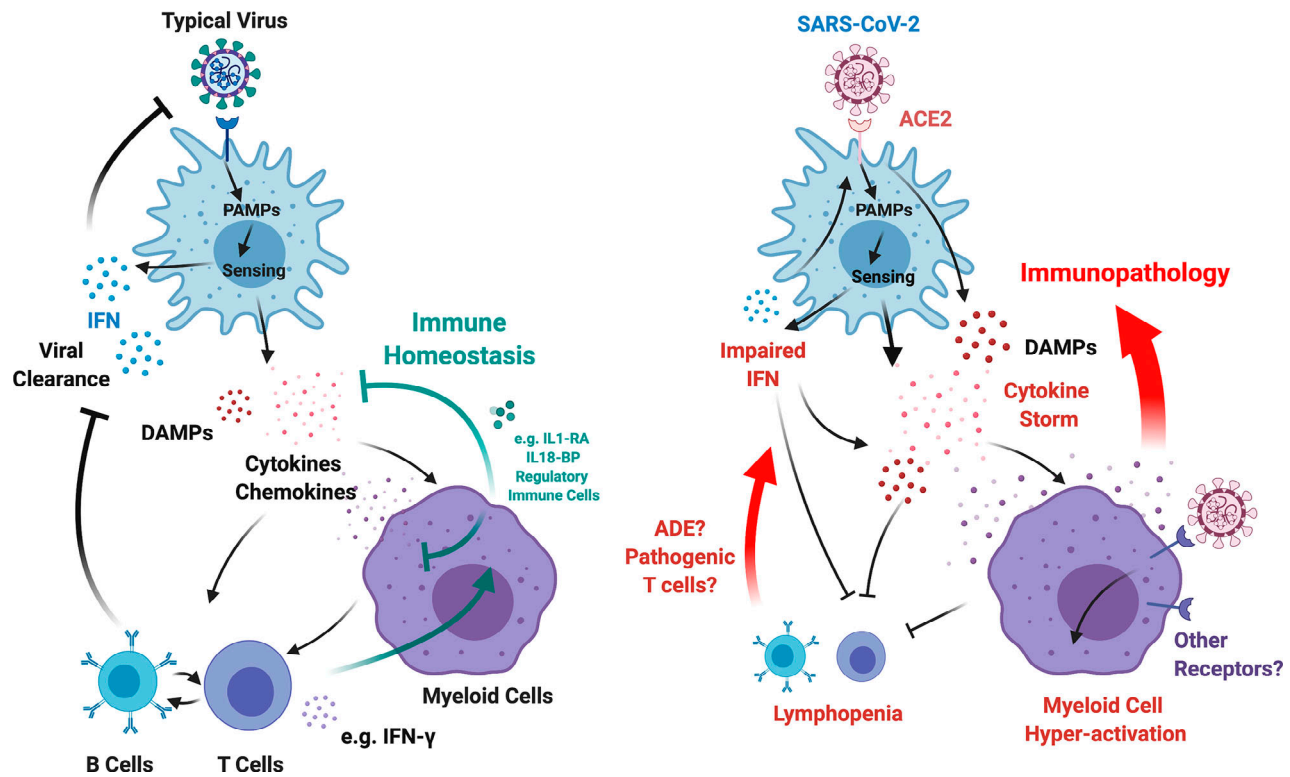


Figure 1. **Asynchronized immune responses in SARS-CoV-2 infection.** Virus infection normally leads to a coordinated immune response (left), from immune activation via PAMPs or DAMPs and numerous cytokines and chemokines, to immune resolution via secretion of natural antagonists, and the downregulation of innate immunity by adaptive immunity as well as by regulatory immune cells. In SARS-CoV-2 infection (right), aberrant innate sensing, alarming, cytokine production, and hyperactivation of myeloid cells triggered through viral–host interactions lead to immunopathology and lymphopenia.

inflammation. In addition to this temporal regulation, spatial considerations also affect the outcome of an immune response (Dorward et al., 2020). Because of their different homeostatic requirements, different organs are differentially immunologically poised; lungs, for example, are more prone to T helper cell 2 (Th2) immunity, mediated in part by unique tissue-resident immune cells and diverse tissue factors that also influence local priming (Ardain et al., 2020).

This synchronized antiviral, intercellular coordination is reinforced by intracellular regulation and enacted via intermolecular interactions. Brakes for the immune system present themselves at an intrinsic level, with some immune cells possessing a short lifespan (e.g., neutrophils), a poor capacity to proliferate (e.g., some tissue-resident macrophages), or a sensitivity to activation-induced cell death (e.g., lymphocytes). Immune responses are also controlled externally by a multitude of costimulatory (e.g., CD28, 4-1BB) and coinhibitory (e.g., PD-1, CTLA-4, LAG-3) receptor–ligand interactions and cytokine/chemokine networks (Chen and Flies, 2013). Many of these inhibitory pathways are induced in response to inflammation to tame the immune response: for example, the secretion of decoy receptors such as IL-1Ra or IL-18BP (Dinarello et al., 2013; Mantovani et al., 2019) in response to IFN- γ (Hurgin et al., 2002; Tilg et al., 1993). Thus, immune homeostasis is achieved via cross-talk between molecules that is integrated within and across innate and adaptive immune cells, ensuring appropriate timing, location, quality, and quantity of a successful antiviral immune response.

COVID-19 immunopathogenesis: An immune asynchrony model

Postmortem analysis of COVID-19 patients showed a heavy infiltration of mononuclear cells in affected areas, including lung, heart, and kidney, coupled with cytokine storm and lymphopenia (Merad and Martin, 2020; Tian et al., 2020). While the underlying cause of pathology remains unclear, below we summarize unique features of SARS-CoV-2 and potential immunological asynchronies that may drive aberrant hyperinflammation (Fig. 1).

Virus entry

Pathogenic human coronaviruses may initially overwhelm the body owing to their efficient entry into lung epithelial cells via ACE2 and rapid replication rates (Chu et al., 2020). ACE2 can also play an immunomodulatory role, serving as a protector against acute lung injury and inflammation in SARS-CoV (Kuba et al., 2005; Li, 2016). Moreover, its more established role as a negative regulator of angiotensin II in the renin-angiotensin system may also lead to pathology, as Ang-II infusion has been shown to increase plasma cytokine levels (e.g., IL-6, IL-1, and TNF- α ; Zhang et al., 2009; Eguchi et al., 2018) and aggravate hypertension, the top comorbidity associated with COVID-19 (Richardson et al., 2020).

Under the pressures of the host–virus arms race, many viruses have adapted to use multiple receptors for entry, and recent studies suggest the existence of additional receptors

involved in SARS-CoV-2 cellular entry. Neuropilin-1 was found to potentiate SARS-CoV-2 infectivity, though this binding was mainly ACE2 dependent (Cantuti-Castelvetri et al., 2020 Preprint; Daly et al., 2020 Preprint). Recent data revealed the existence of SARS-CoV-2 in some immune cell populations, such as myeloid and T cells, that express little ACE2 (Chua et al., 2020). While viruses may enter immune cells through direct phagocytosis or the antibody-dependent enhancement (ADE) effect, not all immune cells (e.g., T cells) are capable of phagocytosis, and the extent and importance of ADE to immune dysregulation remains unknown (Vabret et al., 2020). Moreover, a recent D614G mutation in SARS-CoV-2 that is uninvolved in ACE2 binding has been shown to increase infectivity (Zhang et al., 2020 Preprint). In light of all this evidence, it is possible that novel SARS-CoV-2 receptors on immune cells could exist and are responsible for virus-induced immune dysregulation. The contribution of glycosylation to virus binding also warrants further investigation, as the high glycosylation profile of SARS-CoV-2 has been well documented, involving more than a dozen of N- or O-glycosylation sites. It has been suggested that the virus spike glycosylation constitutes a “glycan mask” to reduce viral immunogenicity (Walls et al., 2016); however, their roles in viral evasion, receptor binding, and immune modulation remain an unclear but important factor in infection.

After receptor binding, the virus gains access to the host cytosol through intracellular protease-mediated proteolytic cleavage of virus spike protein. While proteases such as TMPRSS2 and cathepsin are used by both SARS-CoV-2 and SARS-CoV (Hoffmann et al., 2020), virus spike protein cleavage by furin is unique to SARS-CoV-2 owing to the presence of a polybasic site at the SARS-CoV-2 S1–S2 junction (Xia et al., 2020). With a broader tissue expression compared to TMPRSS2, which is more restricted to epithelial cells (Vaarala et al., 2001), the ability to use furin may result in increased depth and breadth of SARS-CoV-2 pathogenesis compared with SARS-CoV. Thus, SARS-CoV-2 infection is extended spatially not only by receptor expression but also by protease expression and function. It will be important to systematically explore whether other factors facilitate viral infection through ACE2 or other receptors.

Innate viral sensing and myeloid dysregulation

Coronaviruses have evolutionarily developed mechanisms to counteract innate sensing mechanisms (Merad and Martin, 2020; Perlman and Dandekar, 2005). Studies have shown that SARS-CoV-infected mice exhibit a delayed type I IFN response (Channappanavar et al., 2016), which may allow for initial, high rates of viral replication. Many SARS-CoV proteins (Vabret et al., 2020), some of which are conserved in SARS-CoV-2, act as antagonists for IFN and other innate sensing elements, such as inhibition of IRF-3 or RIG-I (Hu et al., 2017; Kopecky-Bromberg et al., 2007). These mechanisms may explain the low amounts of IFN observed in the peripheral blood and lungs of patients with severe COVID-19 (Blanco-Melo et al., 2020; Hadjadj et al., 2020), although this role is somewhat controversial, as elevated levels have been observed in other reports (Lee et al., 2020; Zhou et al., 2020b). Type I IFN initiated by

PAMP signals can further activate inflammatory monocytes, macrophages (Channappanavar et al., 2016), and neutrophils (Middleton et al., 2020; Zuo et al., 2020). Moreover, sustained IFN signaling also up-regulates ACE2 expression (Ziegler et al., 2020), serving as a deadly feed-forward loop exploited by the virus for increased infectivity. Rapid viral replication may activate inflammasome signaling or increase cytopathy of target cells, leading to increased DAMP signaling induced by numerous danger signals (e.g., HMGB1 and heat shock protein), as well as innate immune cytokines (e.g., IL-6, IL-1, IL-18, and GM-CSF). Excessive production of IL-1 and IL-18 may also result from the inflammasome-pyroptosis pathway, as conserved envelope and ORF3a proteins are capable of directly activating the NLRP3 inflammasome (Cagliani et al., 2020; Shah, 2020).

The dysregulation of adaptive immunity

Lymphopenia has also been observed in severe COVID-19 patients (Fig. 2; Vabret et al., 2020). While the cause is unknown, proinflammatory cytokines, such as IL-1, IL-6, GM-CSF, and CSF1 (M-CSF), are capable of directly acting on hematopoietic progenitors, polarizing differentiation to the myeloid lineage in a process called “emergency myelopoiesis,” which may compete with lymphoid differentiation (Boettcher and Manz, 2016). In addition, impaired and delayed type I IFN signaling may hinder recruitment and activation of adaptive immunity (Channappanavar et al., 2014). Some of these cytokines, such as IL-6 and IL-8, have been shown to inhibit dendritic cell priming of naive T cells (Yoshikawa et al., 2009). Of the T cells that remain, a hyperactive and exhausted phenotype with coinhibitory molecule expression (e.g., PD-1, TIGIT, and CTLA-4) is observed (Zheng et al., 2020), with increased populations of potentially pathogenic Th17 cells (Xu et al., 2020). These attenuated yet sustained adaptive immune responses may be pathological, for example via potential activation of bystander T cells that cause organ damage and epitope spreading (Fujinami et al., 2006; Kim and Shin, 2019; Whiteside et al., 2018). Delayed IFN or Fas/FasL signaling may trigger apoptosis of virus-specific T cells in activation-induced cell death, as suggested in SARS-CoV-2-infected spleens and LNs (Chen et al., 2020 Preprint). Other potential mechanisms for lymphopenia include the direct viral infection of lymphocytes (Gu et al., 2005), lymphocyte exhaustion (Diao et al., 2020), relocation to other tissue sites, or suppression from other immune cells, perhaps through interactions with tolerogenic mixed M2 myeloid populations attempting to repair wounded tissue. However, many of these mechanisms are currently speculative, and more evidence is required for further validation. Overall, the suspended arrival of adaptive immunity has many consequences, including ineffective viral clearance along with a failure to temper innate immune responses, as typical innate negative feedback regulators, such as cytokine antagonists IL-1Ra or IL-18BP, are largely induced by IFN- γ released by activated lymphocytes.

Lymphopenia may also cause poor immunological memory, especially regarding memory B cell antibody responses, likely due to lack of T cell help and declining B cell levels in infected patients. In the case of SARS-CoV-2, infected patients have been shown to lose antibody titers within weeks or months after

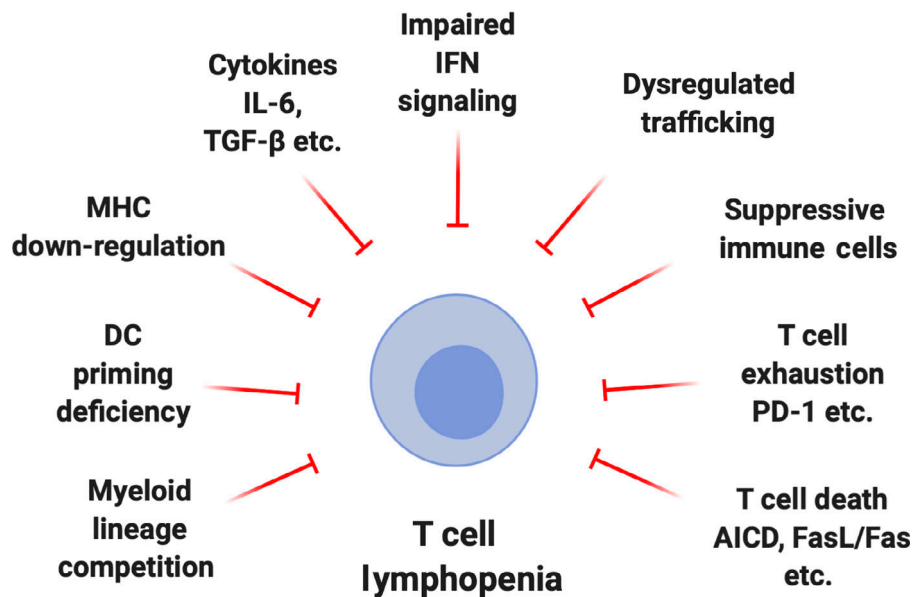


Figure 2. Potential mechanisms of SARS-CoV-2-induced lymphopenia. Lymphopenia is a hallmark of SARS-CoV-2 infection and is influenced by many factors, ranging from those affecting generation to recruitment, function, and survival. AICD, activation-induced cell death; DC, dendritic cell.

recovery (Liu et al., 2020 Preprint; Long et al., 2020), though this also may be attributed to a naturally contracting antibody response after infection. The full breadth of the antibody repertoire must be carefully evaluated, as not all antibodies generated are beneficial in virus neutralization (Iwasaki and Yang, 2020). Antibodies in SARS-CoV have also been shown to be pathological by skewing macrophage responses, leading to fatal acute lung injury through hypercytokinemia (Liu et al., 2019).

Other factors

Intrinsic Th2-focused pulmonary immunity, and perhaps the dysregulation of M2-like macrophages and their cytokine profiles (e.g., IL-10 and TGF- β), may have the potential to increase scarring and fibrosis in COVID-19 patients compared with non-COVID-19-related ARDS. The wound healing process is also intimately linked to blood coagulation, as patients with severe COVID-19 often present with elevated levels of D-dimer, thrombosis, and fibrin/fibrinogen degradation products (Connors and Levy, 2020). Key regulators of the coagulation process have been associated with disease and affect the immune system (Gupta et al., 2020 Preprint); for example, the prothrombinase fibrinogen-like protein 2 is induced in murine coronavirus and causes fibrin deposition (Marsden et al., 2003) while also serving as an immunosuppressive factor for regulatory T cell functionality (Shalev et al., 2008). Vascular leakage from the dysfunction of endothelial cells may also contribute to coagulopathy and promote inflammation (Teuwen et al., 2020).

Potential immunotherapies

In earlier stages of disease, the focus should be on antiviral therapy, but treatment strategies in the late stage of disease should focus on immunosuppression to alleviate immunopathology, given that CRS and ARDS are the dominant causes of death in severe COVID-19 (Fig. 3). To avoid destroying antiviral immunity, key pathways must be identified to correct the dysregulated immune response, with a special emphasis on targeting hyperactivated innate dysregulation. With the recent

modest effect of anti-IL-6 in clinical trials (Atal and Fatima, 2020), we here propose other potential pathways with a mechanistic basis that warrant attention.

Innate immune targets

Correction of the dysregulated innate immune sensing and alarming mechanisms may prove helpful to alleviate COVID-19 pathogenesis, such as inhibitors of the inflammasome and pyroptosis (Yap et al., 2020) or quelling DAMP signaling through agents such as anti-HMGB1 and CD24-Fc (Andersson et al., 2020; Tian et al., 2020). IL-1 family cytokines in particular are up-regulated and act as key mediators of early myeloid over-activation, lung inflammation, and fibrosis (Borthwick, 2016; Conti et al., 2020; George et al., 2020; Huang et al., 2005). Moreover, IL-18 treatment in mouse models causes severe pneumonitis, especially in the context of IL-2 (Okamoto et al., 2002), reminiscent of the features of COVID-19. COVID-19-induced lymphopenia and suppression of IFN- γ secretion may lead to delayed or impaired production of IL-1Ra and IL-18BP, the natural inhibitors of this pathway that are up-regulated in response to IFN- γ . While one study has suggested high levels of IL-1Ra in patients with severe infection (Yang et al., 2020 Preprint), pathology may arise from delayed secretion of receptor antagonists that is missed by collecting data at a single time point. Detailed, longitudinal measurement of free IL-1 and IL-18 and their natural antagonists may provide biomarker candidates for COVID-19 patients and present possible opportunities for therapeutic intervention.

Other pathways that affect myeloid cell activation and cytokine secretion are also worth consideration. Small, conditional RNA sequencing analysis of COVID-19 samples indicated that CSF-1 and CSF-2 may be associated with CRS (Wen et al., 2020). A key growth factor for macrophages, the CSF-1/CSF1-R pathway plays an important role in pulmonary fibrosis, with aberrant expression observed in a subset of COVID-19 patients (George et al., 2020). In addition, IL-8, a proinflammatory chemokine for neutrophils as well as macrophages and lymphocytes,

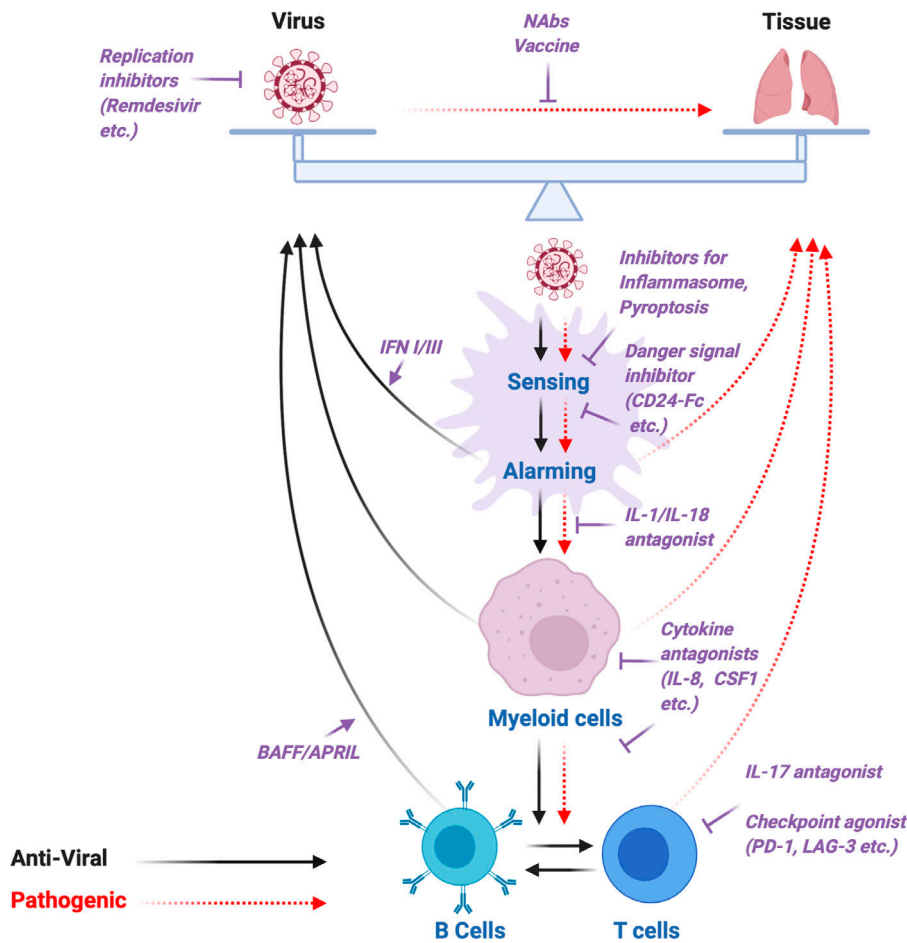


Figure 3. Strategies for COVID-19 therapeutic intervention. Dysregulations at every stage of the antiviral response can be corrected but must carefully balance viral clearance with host toxicity. In early stages of the disease, the focus should be on prophylactic vaccines and antiviral drugs, while in late stages of the disease, various immunomodulatory agents should be considered to calm a hysteric innate immune response, down-regulate pathogenic T cells, and boost productive B cell antibody responses. NAb, neutralizing antibodies.

correlated with disease severity in COVID-19 and SARS (Gong et al., 2020 Preprint; Wang et al., 2004; Wong et al., 2004), serving as the rationale for an ongoing clinical trial with anti-IL-8. Efforts are also underway to target other cytokines (e.g., anti-GM-CSF; Lang et al., 2020) and signaling pathways (e.g., JAK-STAT and IRAK4 inhibitors) activated in the innate immune population.

Adaptive immune targets

T cells are critical for viral clearance but also cause pathology. While stimulators of adaptive immunity may be beneficial in the earlier stages of disease to optimize antiviral defense, we advocate for the use of negative T cell regulators in severe COVID-19 patients to combat hyperinflammation in the late stage of disease. Immunosuppression cannot be too general at the risk of destroying antiviral immunity; thus, it is important to specifically dampen the activity of pathogenic T cells while sparing naive T cells. Drugs such as CTLA4-Ig (Abatacept), which blocks CD28 interactions and more affects naive T cells, may not be a good option for COVID-19 treatment. Other coinhibitory pathways, such as PD-1 and LAG-3, are up-regulated on antigen-experienced cells and may be more virus specific. Anti-PD-1 antagonist therapies are currently being tested in a phase II clinical trial, under the rationale that anti-PD blockade may compensate for T cell depletion; however, caution should be exercised regarding anti-PD in COVID-19, as anti-PD-1 treatment

has induced lethal pneumonia in cancer patients (Nishino et al., 2015). Although agonists for the PD-L1/PD-1 pathway have not yet been successful, agonists for other coinhibitory pathways, such as LAG-3 and VISTA, exist in the form of agonistic antibody and/or natural ligand (Grebinski and Vignali, 2020; Prodeus et al., 2017; Wang et al., 2019). Given the pathogenic Th17 signature, RORγt and RORα inhibitors, or anti-IL-17 and anti-IL-17R blockade, may also prove useful for treatment.

Declining B cell numbers and function in patients can potentially be corrected via boosting T cell help (e.g., targeting the CD40/CD40L interaction) or by directly supporting germinal center B cells and long-lived plasma or memory B cell responses (e.g., BAFF or APRIL). However, care must be taken to not increase inflammation while supporting B cell antibody responses, especially as the quality and quantity of the antibody repertoire can be difficult to control. The use of vaccines and neutralizing antibodies has been considered the most promising long-term strategy to prevent further outbreaks of SARS-CoV-2. Dozens of vaccine programs, including intact inactivated and attenuated virus vaccines and virus-based subunits of virion structural proteins or nucleic acids (DNA/RNA) vaccines, are currently underway, some of which have shown initial encouraging data in generating neutralizing antibody titers and/or T cell responses in humans (Jackson et al., 2020; Keech et al., 2020 Preprint; Mulligan et al., 2020; Zhu et al., 2020). However, the quality and quantity of the antiviral antibody response over time

awaits further evaluation. The use of convalescent plasma is another approach, although there are significant challenges regarding its supply, quality, and dosing regimen (Abraham, 2020). Other than these approaches, therapeutic antibody programs mostly target the receptor binding domain to block the SARS-CoV-2 spike/ACE2 interaction; however, antibodies targeting spike epitopes outside of the receptor binding domain were found to be functional in decreasing viral infection (Chi et al., 2020). Given that the virus binds immune cells that lack expression of ACE2, there is also an urgent need to identify additional viral receptors, especially those that are functionally involved in COVID-19 immunopathogenesis, for the design of antibody cocktails or multispecific antibodies that block all viral–host interactions. Rational antibody engineering should be undertaken to prevent virus mutational escape (Baum et al., 2020), and antibody affinity, Fc-mediated effector function, and possible ADE should also be considered as important factors in therapeutic design.

Conclusion

Overall, a hyperactive innate immune system coupled with an asynchronized and inadequate adaptive immune system result in a cacophony of severe tissue damage without viral clearance and immunological resolution. From this overall picture of viral pathogenesis, a general strategy for COVID-19 treatment emerges, consisting of controlling the virus at the early stage of disease and taming the immune system at the late stage of disease. The necessity of large-scale and carefully controlled clinical trials to properly identify disease biomarkers and evaluate efficacy of potential therapeutics cannot be overstated. In addition, the discovery of novel receptors for viral entry and immune dysregulation will lead to the reevaluation of proposed neutralizing antibodies and highlights the urgency for further research on critical viral immune interactions to identify key regulators for clinical use.

Acknowledgments

We thank Drs. Xu Zhou and Siyuan Ding for critically editing the paper and all Jun Wang Lab members for helpful discussion.

Author contributions: J. Wang, T. Zhou, T.T. Su, and T. Mudianto conceived the study and wrote the manuscript.

Disclosures: The authors declare no competing interests exist.

Submitted: 7 July 2020

Revised: 26 August 2020

Accepted: 28 August 2020

References

Abraham, J. 2020. Passive antibody therapy in COVID-19. *Nat. Rev. Immunol.* 20:401–403. <https://doi.org/10.1038/s41577-020-0365-7>

Andersson, U., W. Ottestad, and K.J. Tracey. 2020. Extracellular HMGB1: a therapeutic target in severe pulmonary inflammation including COVID-19? *Mol. Med.* 26:42. <https://doi.org/10.1186/s10020-020-00172-4>

Ardain, A., M.J. Marakalala, and A. Leslie. 2020. Tissue-resident innate immunity in the lung. *Immunology.* 159:245–256. <https://doi.org/10.1111/imm.13143>

Atal, S., and Z. Fatima. 2020. IL-6 Inhibitors in the Treatment of Serious COVID-19: A Promising Therapy? *Pharmaceut. Med.* 34:223–231.

Baum, A., B.O. Fulton, E. Wloga, R. Copin, K.E. Pascal, V. Russo, S. Giordano, K. Lanza, N. Negron, M. Ni, et al. 2020. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science.* 369:1014–1018.

Blanco-Melo, D., B.E. Nilsson-Payant, W.C. Liu, S. Uhl, D. Hoagland, R. Møller, T.X. Jordan, K. Oishi, M. Panis, D. Sachs, et al. 2020. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell.* 181:1036–1045.e9. <https://doi.org/10.1016/j.cell.2020.04.026>

Boettcher, S., and M.G. Manz. 2016. Sensing and translation of pathogen signals into demand-adapted myelopoiesis. *Curr. Opin. Hematol.* 23: 5–10. <https://doi.org/10.1097/MOH.0000000000000201>

Borthwick, L.A. 2016. The IL-1 cytokine family and its role in inflammation and fibrosis in the lung. *Semin. Immunopathol.* 38:517–534. <https://doi.org/10.1007/s00281-016-0559-z>

Bost, P., A. Giladi, Y. Liu, Y. Bendjelal, G. Xu, E. David, R. Blecher-Gonen, M. Cohen, C. Medaglia, H. Li, et al. 2020. Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients. *Cell.* 181:1475–1488.e12. <https://doi.org/10.1016/j.cell.2020.05.006>

Cagliani, R., D. Forni, M. Clerici, and M. Sironi. 2020. Coding potential and sequence conservation of SARS-CoV-2 and related animal viruses. *Infect. Genet. Evol.* 83. 104353. <https://doi.org/10.1016/j.meegid.2020.104353>

Cantuti-Castelvetri, L., R. Ojha, L.D. Pedro, M. Djannatian, J. Franz, S. Kivivanen, K. Kallio, T. Kaya, M. Anastasina, T. Smura, et al. 2020. Neuropilin-1 facilitates SARS-CoV-2 cell entry and provides a possible pathway into the central nervous system. *bioRxiv.* <https://doi.org/10.1101/2020.06.07.137802> (Preprint posted July 15, 2020).

Channappanavar, R., A.R. Fehr, R. Vijay, M. Mack, J. Zhao, D.K. Meyerholz, and S. Perlman. 2016. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe.* 19:181–193. <https://doi.org/10.1016/j.chom.2016.01.007>

Channappanavar, R., J. Zhao, and S. Perlman. 2014. T cell-mediated immune response to respiratory coronaviruses. *Immunol. Res.* 59:118–128. <https://doi.org/10.1007/s12026-014-8534-z>

Chen, L., and D.B. Flies. 2013. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat. Rev. Immunol.* 13:227–242. <https://doi.org/10.1038/nri3405>

Chen, Y., Z. Feng, B. Diao, R. Wang, G. Wang, C. Wang, Y. Tan, L. Liu, C. Wang, Y. Liu, et al. 2020. The Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Directly Decimates Human Spleens and Lymph Nodes. *medRxiv.* <https://doi.org/10.1101/2020.03.27.20045427> (Preprint posted March 31, 2020).

Chi, X., R. Yan, J. Zhang, G. Zhang, Y. Zhang, M. Hao, Z. Zhang, P. Fan, Y. Dong, Y. Yang, et al. 2020. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. *Science.* 369: 650–655. <https://doi.org/10.1126/science.abc6952>

Chu, H., J.F.-W. Chan, T.T.-T. Yuen, H. Shuai, S. Yuan, Y. Wang, B. Hu, C.C.-Y. Yip, J.O.-L. Tsang, X. Huang, et al. 2020. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. *Lancet Microbe.* 1:e14–e23. [https://doi.org/10.1016/S2666-5247\(20\)30004-5](https://doi.org/10.1016/S2666-5247(20)30004-5)

Chua, R.L., S. Lukassen, S. Trump, B.P. Hennig, D. Wendisch, F. Pott, O. Debnath, L. Thürmann, F. Kurth, M.T. Völker, et al. 2020. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat. Biotechnol.* 38:970–979. <https://doi.org/10.1038/s41587-020-0602-4>

Connors, J.M., and J.H. Levy. 2020. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 135:2033–2040. <https://doi.org/10.1182/blood.2020006000>

Conti, P., G. Ronconi, A. Caraffa, C.E. Gallenga, R. Ross, I. Frydas, and S.K. Kritas. 2020. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J. Biol. Regul. Homeost. Agents.* 34:327–331.

Daly, J.L., B. Simonetti, C. Antón-Plágaro, M. Kavanagh Williamson, D.K. Shoemark, L. Simón-Gracia, K. Klein, M. Bauer, R. Hollandi, U.F. Greber, et al. 2020. Neuropilin-1 is a host factor for SARS-CoV-2 infection. *bioRxiv.* <https://doi.org/10.1101/2020.06.05.134114> (Preprint posted June 5, 2020).

Diao, B., C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, L. Chen, M. Li, Y. Liu, G. Wang, et al. 2020. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Front. Immunol.* 11: 827. <https://doi.org/10.3389/fimmu.2020.00827>

- Dinareello, C.A., D. Novick, S. Kim, and G. Kaplanski. 2013. Interleukin-18 and IL-18 binding protein. *Front. Immunol.* 4:289. <https://doi.org/10.3389/fimmu.2013.00289>
- Dorward, D.A., C.D. Russell, I.H. Um, M. Elshani, S.D. Armstrong, R. Penrice-Randal, T. Millar, C.E. Lerpiniere, G. Tagliavini, C.S. Hartley, et al. 2020. Tissue-specific tolerance in fatal Covid-19. *medRxiv*. <https://doi.org/10.1101/2020.07.02.20145003> (Preprint posted July 4, 2020).
- Eguchi, S., T. Kawai, R. Scalia, and V. Rizzo. 2018. Understanding Angiotensin II Type 1 Receptor Signaling in Vascular Pathophysiology. *Hypertension*. 71:804–810. <https://doi.org/10.1161/HYPERTENSIONAHA.118.10266>
- Fujinami, R.S., M.G. von Herrath, U. Christen, and J.L. Whitton. 2006. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. *Clin. Microbiol. Rev.* 19:80–94. <https://doi.org/10.1128/CMR.19.1.80-94.2006>
- George, P.M., A.U. Wells, and R.G. Jenkins. 2020. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir. Med.* 8:807–815. [https://doi.org/10.1016/S2213-2600\(20\)30225-3](https://doi.org/10.1016/S2213-2600(20)30225-3)
- Gong, J., H. Dong, S.Q. Xia, Y.Z. Huang, D. Wang, Y. Zhao, W. Liu, S. Tu, M. Zhang, Q. Wang, and F. Lu. 2020. Correlation Analysis Between Disease Severity and Inflammation-related Parameters in Patients with COVID-19 Pneumonia. *medRxiv*. <https://doi.org/10.1101/2020.02.25.20025643> (Preprint posted February 27, 2020).
- Grebinoski, S., and D.A. Vignali. 2020. Inhibitory receptor agonists: the future of autoimmune disease therapeutics? *Curr. Opin. Immunol.* 67:1–9. <https://doi.org/10.1016/j.coi.2020.06.001>
- Gu, J., E. Gong, B. Zhang, J. Zheng, Z. Gao, Y. Zhong, W. Zou, J. Zhan, S. Wang, Z. Xie, et al. 2005. Multiple organ infection and the pathogenesis of SARS. *J. Exp. Med.* 202:415–424. <https://doi.org/10.1084/jem.20050828>
- Guan, W.J., Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei, D.S.C. Hui, et al; China Medical Treatment Expert Group for Covid-19. 2020. Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* 382:1708–1720. <https://doi.org/10.1056/NEJMoa2002032>
- Gupta, V., S. Haider, M. Verma, K. Ponnusamy, M.Z. Malik, N. Singhvi, H. Verma, R. Kumar, U. Sood, P. Hira, et al. 2020. Multi-Omics and Integrated Network Approach to Unveil Evolutionary Patterns, Mutational Hotspots, Functional Crosstalk and Regulatory Interactions in SARS-CoV-2. *bioRxiv*. <https://doi.org/10.1101/2020.06.20.162560> (Preprint posted June 20, 2020).
- Hadjadi, J., N. Yatim, L. Barnabei, A. Corneau, J. Boussier, N. Smith, H. Péré, B. Charbit, V. Bondet, C. Chenevier-Gobeaux, et al. 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 369:718–724. <https://doi.org/10.1126/science.abc6027>
- Hoffmann, M., H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, et al. 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 181:271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
- Hu, Y., W. Li, T. Gao, Y. Cui, Y. Jin, P. Li, Q. Ma, X. Liu, and C. Cao. 2017. The Severe Acute Respiratory Syndrome Coronavirus Nucleocapsid Inhibits Type I Interferon Production by Interfering with TRIM25-Mediated RIG-I Ubiquitination. *J. Virol.* 91. e02143-16. <https://doi.org/10.1128/JVI.02143-16>
- Huang, K.J., I.J. Su, M. Theron, Y.C. Wu, S.K. Lai, C.C. Liu, and H.Y. Lei. 2005. An interferon-gamma-related cytokine storm in SARS patients. *J. Med. Virol.* 75:185–194. <https://doi.org/10.1002/jmv.20255>
- Hurgin, V., D. Novick, and M. Rubinstein. 2002. The promoter of IL-18 binding protein: activation by an IFN- γ -induced complex of IFN regulatory factor 1 and CCAAT/enhancer binding protein β . *Proc. Natl. Acad. Sci. USA*. 99:16957–16962. <https://doi.org/10.1073/pnas.262663399>
- Iwasaki, A., and Y. Yang. 2020. The potential danger of suboptimal antibody responses in COVID-19. *Nat. Rev. Immunol.* 20:339–341. <https://doi.org/10.1038/s41577-020-0321-6>
- Jackson, L.A., E.J. Anderson, N.G. Roupael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, et al; mRNA-1273 Study Group. 2020. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa2022483>
- Keech, C., G. Albert, P. Reed, S. Neal, J.S. Plested, M. Zhu, S. Cloney-Clark, H. Zhou, N. Patel, M.B. Frieman, et al. 2020. First-in-Human Trial of a SARS-CoV 2 Recombinant Spike Protein Nanoparticle Vaccine. *medRxiv*. <https://doi.org/10.1101/2020.08.05.20168435> (Preprint posted August 6, 2020).
- Kim, T.S., and E.C. Shin. 2019. The activation of bystander CD8⁺ T cells and their roles in viral infection. *Exp. Mol. Med.* 51:1–9.
- Kim, K.D., J. Zhao, S. Auh, X. Yang, P. Du, H. Tang, and Y.-X. Fu. 2007. Adaptive immune cells temper initial innate responses. *Nat. Med.* 13:1248–1252. <https://doi.org/10.1038/nm1633>
- Koch, J., A. Steinle, C. Watzl, and O. Mandelboim. 2013. Activating natural cytotoxicity receptors of natural killer cells in cancer and infection. *Trends Immunol.* 34:182–191. <https://doi.org/10.1016/j.it.2013.01.003>
- Kopecky-Bromberg, S.A., L. Martínez-Sobrido, M. Frieman, R.A. Baric, and P. Palese. 2007. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. *J. Virol.* 81:548–557. <https://doi.org/10.1128/JVI.01782-06>
- Kuba, K., Y. Imai, S. Rao, et al. 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* 11:875–879. <https://doi.org/10.1038/nm1267>
- Lang, F.M., K.M.C. Lee, J.R. Tejjaro, B. Becher, and J.A. Hamilton. 2020. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat. Rev. Immunol.* 20:507–514. <https://doi.org/10.1038/s41577-020-0357-7>
- Lee, J.S., S. Park, H.W. Jeong, J.Y. Ahn, S.J. Choi, H. Lee, B. Choi, S.K. Nam, M. Sa, J.S. Kwon, et al. 2020. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci. Immunol.* 5. eabd1554. <https://doi.org/10.1126/sciimmunol.abd1554>
- Lescure, F.-X., L. Bouadma, D. Nguyen, M. Parisey, P.-H. Wicky, S. Behillil, A. Gaymard, M. Bouscambert-Duchamp, F. Donati, Q. Le Hingrat, et al. 2020. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect. Dis.* 20:697–706. [https://doi.org/10.1016/S1473-3099\(20\)30200-0](https://doi.org/10.1016/S1473-3099(20)30200-0)
- Li, F. 2016. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annu. Rev. Virol.* 3:237–261. <https://doi.org/10.1146/annurev-virology-110615-042301>
- Liu, L., Q. Wei, Q. Lin, J. Fang, H. Wang, H. Kwok, H. Tang, K. Nishiura, J. Peng, Z. Tan, et al. 2019. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight*. 4. e123158. <https://doi.org/10.1172/jci.insight.123158>
- Liu, T., S. Wu, H. Tao, G. Zeng, F. Zhou, F. Guo, and X. Wang. 2020. Prevalence of IgG antibodies to SARS-CoV-2 in Wuhan - implications for the ability to produce long-lasting protective antibodies against SARS-CoV-2. *medRxiv*. <https://doi.org/10.1101/2020.06.13.20130252> (Preprint posted June 16, 2020).
- Long, Q.-X., X.-J. Tang, Q.-L. Shi, Q. Li, H.-J. Deng, J. Yuan, J.-L. Hu, W. Xu, Y. Zhang, F.-J. Lv, et al. 2020. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat. Med.* 26:1200–1204. <https://doi.org/10.1038/s41591-020-0965-6>
- Mantovani, A., C.A. Dinareello, M. Molgora, and C. Garlanda. 2019. Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity. *Immunity*. 50:778–795. <https://doi.org/10.1016/j.immuni.2019.03.012>
- Marsden, P.A., Q. Ning, L.S. Fung, X. Luo, Y. Chen, M. Mendicino, A. Ghanekar, J.A. Scott, T. Miller, C.W.Y. Chan, et al. 2003. The Fgl2/fibrinolytic prothrombinase contributes to immunologically mediated thrombosis in experimental and human viral hepatitis. *J. Clin. Invest.* 112:58–66. <https://doi.org/10.1172/JCI18114>
- Merad, M., and J.C. Martin. 2020. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat. Rev. Immunol.* 20:355–362. <https://doi.org/10.1038/s41577-020-0331-4>
- Middleton, E.A., X.-Y. He, F. Denorme, R.A. Campbell, D. Ng, S.P. Salvatore, M. Mostyka, A. Baxter-Stoltzfus, A.C. Borczuk, M. Loda, et al. 2020. Neutrophil Extracellular Traps (NETs) Contribute to Immuno-thrombosis in COVID-19 Acute Respiratory Distress Syndrome. *Blood*. <https://doi.org/10.1182/blood.2020007008>
- Mulligan, M.J., K.E. Lyke, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, K. Neuzil, V. Raabe, R. Bailey, K.A. Swanson, et al. 2020. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature*. <https://doi.org/10.1038/s41586-020-2639-4>
- Nishino, M., L.M. Sholl, F.S. Hodi, H. Hatabu, and N.H. Ramaiya. 2015. Anti-PD-1-Related Pneumonitis during Cancer Immunotherapy. *N. Engl. J. Med.* 373:288–290. <https://doi.org/10.1056/NEJMc1505197>
- Okamoto, M., S. Kato, K. Oizumi, M. Kinoshita, Y. Inoue, K. Hoshino, S. Akira, A.N. McKenzie, H.A. Young, and T. Hoshino. 2002. Interleukin 18 (IL-18) in synergy with IL-2 induces lethal lung injury in mice: a potential role for cytokines, chemokines, and natural killer cells in the pathogenesis of interstitial pneumonia. *Blood*. 99:1289–1298. <https://doi.org/10.1182/blood.V99.4.1289>
- Perlman, S., and A.A. Dandekar. 2005. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat. Rev. Immunol.* 5:917–927. <https://doi.org/10.1038/nri1732>
- Perlman, S., and J. Netland. 2009. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat. Rev. Microbiol.* 7:439–450. <https://doi.org/10.1038/nrmicro2147>
- Prodeus, A., A. Abdul-Wahid, A. Sparkes, N.W. Fischer, M. Cydzik, N. Chiang, M. Alwash, A. Ferzoco, N. Vacaresse, M. Julius, et al. 2017. VISTA.COMP

- an engineered checkpoint receptor agonist that potently suppresses T cell-mediated immune responses. *JCI Insight*. 2. e94308. <https://doi.org/10.1172/jci.insight.94308>
- Richardson, S., J. Hirsch, M. Narasimhan, et al; and the Northwell COVID-19 Research Consortium. 2020. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 323:2052-2059. <https://doi.org/10.1001/jama.2020.6775>
- Sanche, S., Y.T. Lin, C. Xu, E. Romero-Severson, N. Hengartner, and R. Ke. 2020. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg. Infect. Dis.* 26:1470-1477. <https://doi.org/10.3201/eid2607.200282>
- Shah, A. 2020. Novel Coronavirus-Induced NLRP3 Inflammasome Activation: A Potential Drug Target in the Treatment of COVID-19. *Front. Immunol.* 11:1021. <https://doi.org/10.3389/fimmu.2020.101021>
- Shalev, I., H. Liu, C. Kosciak, A. Bartczak, M. Javadi, K.M. Wong, A. Maknojia, W. He, M.F. Liu, J. Diao, et al. 2008. Targeted deletion of fgl2 leads to impaired regulatory T cell activity and development of autoimmune glomerulonephritis. *J. Immunol.* 180:249-260. <https://doi.org/10.4049/jimmunol.180.1.249>
- Stetson, D.B., and R. Medzhitov. 2006. Type I interferons in host defense. *Immunity*. 25:373-381. <https://doi.org/10.1016/j.immuni.2006.08.007>
- Teuwen, L.-A., V. Geldhof, A. Pasut, and P. Carmeliet. 2020. COVID-19: the vasculature unleashed. *Nat. Rev. Immunol.* 20:389-391. <https://doi.org/10.1038/s41577-020-0343-0>
- Tian, RR., MX. Zhang, M. Liu, et al. 2020. CD24Fc protects against viral pneumonia in simian immunodeficiency virus-infected Chinese rhesus monkeys. *Cell. Mol. Immunol.* 17:887-888. <https://doi.org/10.1038/s41423-020-0452-5>
- Tian, S., Y. Xiong, H. Liu, L. Niu, J. Guo, M. Liao, and S.-Y. Xiao. 2020. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod. Pathol.* 33:1007-1014. <https://doi.org/10.1038/s41379-020-0536-x>
- Tilg, H., J.W. Mier, W. Vogel, W.E. Aulitzky, C.J. Wiedermann, E. Vannier, C. Huber, and C.A. Dinarello. 1993. Induction of circulating IL-1 receptor antagonist by IFN treatment. *J. Immunol.* 150:4687-4692.
- Vaarala, M.H., K.S. Porvari, S. Kellokumpu, A.P. Kyllönen, and P.T. Vihko. 2001. Expression of transmembrane serine protease TMPRSS2 in mouse and human tissues. *J. Pathol.* 193:134-140. [https://doi.org/10.1002/1096-9896\(2000\)9999:9999::AID-PATH743>3.0.CO;2-T](https://doi.org/10.1002/1096-9896(2000)9999:9999::AID-PATH743>3.0.CO;2-T)
- Vabret, N., G.J. Britton, C. Gruber, S. Hegde, J. Kim, M. Kuksin, R. Levantovsky, L. Malle, A. Moreira, M.D. Park, et al; Sinai Immunology Review Project. 2020. Immunology of COVID-19: Current State of the Science. *Immunity*. 52:910-941. <https://doi.org/10.1016/j.immuni.2020.05.002>
- Walls, A.C., M.A. Tortorici, B. Frenz, J. Snijder, W. Li, F.A. Rey, F. DiMaio, B.-J. Bosch, and D. Veelsler. 2016. Glycan shield and epitope masking of a coronavirus spike protein observed by cryo-electron microscopy. *Nat. Struct. Mol. Biol.* 23:899-905. <https://doi.org/10.1038/nsmb.3293>
- Wang, J., M.F. Sanmamed, I. Datar, T.T. Su, L. Ji, J. Sun, L. Chen, Y. Chen, G. Zhu, W. Yin, et al. 2019. Fibrinogen-like Protein 1 Is a Major Immune Inhibitory Ligand of LAG-3. *Cell*. 176:334-347.e12. <https://doi.org/10.1016/j.cell.2018.11.010>
- Wang, W.K., S.Y. Chen, I.J. Liu, C.L. Kao, H.L. Chen, B.L. Chiang, J.T. Wang, W.H. Sheng, P.R. Hsueh, C.F. Yang, et al; Severe Acute Respiratory Syndrome Research Group of the National Taiwan University College of Medicine/NTU Hospital. 2004. Temporal relationship of viral load, ribavirin, interleukin (IL)-6, IL-8, and clinical progression in patients with severe acute respiratory syndrome. *Clin. Infect. Dis.* 39:1071-1075. <https://doi.org/10.1086/423808>
- Wen, W., W. Su, H. Tang, W. Le, X. Zhang, Y. Zheng, X. Liu, L. Xie, J. Li, J. Ye, et al. 2020. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov.* 6:31. <https://doi.org/10.1038/s41421-020-0168-9>
- Whiteside, S.K., J.P. Snook, M.A. Williams, and J.J. Weis. 2018. Bystander T Cells: A Balancing Act of Friends and Foes. *Trends Immunol.* 39: 1021-1035. <https://doi.org/10.1016/j.it.2018.10.003>
- Wong, C.K., C.W. Lam, A.K. Wu, W.K. Ip, N.L. Lee, I.H. Chan, L.C. Lit, D.S. Hui, M.H. Chan, S.S. Chung, et al. 2004. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* 136:95-103. <https://doi.org/10.1111/j.1365-2249.2004.02415.x>
- Xia, S., Q. Lan, S. Su, X. Wang, W. Xu, Z. Liu, Y. Zhu, Q. Wang, L. Lu, and S. Jiang. 2020. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. *Signal Transduct. Target. Ther.* 5:92. <https://doi.org/10.1038/s41392-020-0184-0>
- Xu, Z., L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, et al. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med.* 8:420-422. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
- Yang, Y., C. Shen, J. Li, J. Yuan, M. Yang, F. Wang, G. Li, Y. Li, L. Xing, L. Peng, et al. 2020. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. *medRxiv*. <https://doi.org/10.1101/2020.03.02.20029975> (Preprint posted March 6, 2020).
- Yap, J.K.Y., M. Moriyama, and A. Iwasaki. 2020. Inflammasomes and Pyroptosis as Therapeutic Targets for COVID-19. *J. Immunol.* 205:307-312. <https://doi.org/10.4049/jimmunol.2000513>
- Yoshikawa, T., T. Hill, K. Li, C.J. Peters, and C.T. Tseng. 2009. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J. Virol.* 83: 3039-3048. <https://doi.org/10.1128/JVI.01792-08>
- Zhang, L., C.B. Jackson, H. Mou, A. Ojha, E.S. Rangarajan, T. Izard, M. Farzan, and H. Choe. 2020. The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity. *bioRxiv*. <https://doi.org/10.1101/2020.06.12.148726> (Preprint posted June 12, 2020).
- Zhang, R., Y. Wu, M. Zhao, et al. 2009. Role of HIF-1alpha in the regulation ACE and ACE2 expression in hypoxic human pulmonary artery smooth muscle cells. *Am. J. Physiol. Lung Cell Mol. Physiol.* 297:L631-L640. <https://doi.org/10.1152/ajplung.90415.2008>
- Zheng, H.-Y., M. Zhang, C.-X. Yang, N. Zhang, X.-C. Wang, X.-P. Yang, X.-Q. Dong, and Y.-T. Zheng. 2020. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell. Mol. Immunol.* 17:541-543. <https://doi.org/10.1038/s41423-020-0401-3>
- Zhou, P., X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, et al. 2020a. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 579:270-273. <https://doi.org/10.1038/s41586-020-2012-7>
- Zhou, Z., L. Ren, L. Zhang, J. Zhong, Y. Xiao, Z. Jia, L. Guo, J. Yang, C. Wang, S. Jiang, et al. 2020b. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. *Cell Host Microbe*. 27:883-890.e2. <https://doi.org/10.1016/j.chom.2020.04.017>
- Zhu, F.C., Y.H. Li, X.H. Guan, L.H. Hou, W.J. Wang, J.X. Li, S.P. Wu, B.S. Wang, Z. Wang, L. Wang, et al. 2020. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet*. 395:1845-1854. [https://doi.org/10.1016/S0140-6736\(20\)31208-3](https://doi.org/10.1016/S0140-6736(20)31208-3)
- Ziegler, C.G.K., S.J. Allon, S.K. Nyquist, I.M. Mbanjo, V.N. Miao, C.N. Tzouanas, Y. Cao, A.S. Yousif, J. Bals, B.M. Hauser, et al; HCA Lung Biological Network. 2020. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. *Cell*. 181:1016-1035.e19. <https://doi.org/10.1016/j.cell.2020.04.035>
- Zou, L., F. Ruan, M. Huang, L. Liang, H. Huang, Z. Hong, J. Yu, M. Kang, Y. Song, J. Xia, et al. 2020. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N. Engl. J. Med.* 382:1177-1179. <https://doi.org/10.1056/NEJMc2001737>
- Zuo, Y., S. Yalavarthi, H. Shi, K. Gockman, M. Zuo, J.A. Madison, C. Blair, A. Weber, B.J. Barnes, M. Egeblad, et al. 2020. Neutrophil extracellular traps in COVID-19. *JCI Insight*. 5. e138999.