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An aberrant inflammatory response in severe COVID-19

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Severe COVID-19 arises from the convergence of inadequate pre-existing immunity and a host response that damages, rather than repairs, tissues. We outline clinical presentations of COVID-19 that are likely driven by dysregulated host immunity, discuss potential mechanisms underlying pathological responses, and highlight important areas for basic research on this topic.

The substantial mortality in coronavirus disease 2019 (COVID-19) has been driven largely by an absence of pre-existing immunity that could have provided some protection in vulnerable populations against severe and fatal outcomes. As population immunity increases in some regions, severe COVID-19 has become much less frequent; yet communities lacking protection continue to be ravaged by this disease. In addition to vaccines, having medications that prevent the acute respiratory distress syndrome (ARDS) that is often central in fatal COVID-19 could dramatically reduce the threat of SARS-CoV-2 as a human pathogen. For this reason, understanding mechanisms involved in the pathogenesis of severe COVID-19 is imperative.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections result in a vast spectrum of clinical outcomes, yet most infections are subclinical or mild, even in the absence of pre-existing immunity. The drivers of severe COVID-19 are not entirely clear, but excessive inflammation is nearly always associated with worsening clinical status in this disease. Interestingly, minimal virus is detected in most organs obtained from autopsies of COVID-19 patients, which may suggest that while the virus triggers an initial disease, it is not the ultimate cause of organ failure. Tissue damage often appears driven by excessive accumulation and activation of effector immune cells. Together, the evidence supports a model in which severe and fatal COVID-19 are driven by an aberrant immune response to the infection that causes pathology rather than restoring health. We propose that this aberrant response is the driver of susceptibility to severe COVID-19 in vulnerable populations.

In addition to severe disease, SARS-CoV-2 infections can result in long-term symptoms (here called “long COVID syndromes”) in a large proportion of cases, regardless of severity of the acute infection. Many of the long-term sequelae are likely to be driven by inflammatory pathways. In this article, we outline clinical presentations of COVID-19 that are likely driven by dysregulated host immune responses and discuss potential mechanisms of disease as well as outstanding clinical and research questions on this important topic.

COVID-19 clinical presentations and syndromes related to inflammation

Severe acute COVID-19
Those who develop severe COVID-19 usually worsen after 7 days of mild-to-moderate symptoms. Many of the sequelae in severe cases, such as ARDS, thromboembolism, arrhythmias, and renal failure, are mediated by inflammation and are central in the mortality associated with COVID-19. Some effective treatments have immunomodulatory or immunosuppressive effects. These include compounds with data showing clinical benefit such as corticosteroids, tocilizumab that inhibits the proinflammatory cytokine interleukin-6 (IL-6), the JAK inhibitor baricitinib, and SARS-CoV-2 monoclonal antibodies (mAbs). While we know that severe COVID-19 is associated with an elevation in routine inflammatory markers and an absence of early neutralizing antibodies, we currently lack adequate tools to identify cases that would benefit from early therapeutic interventions. Further, methods are not yet established for guiding treatments based on monitoring of inflammation within affected organs, short of invasive biopsies. As an example, the assessment of lung bronchoscopy fluid for cellular and soluble factors could be very helpful for therapeutic monitoring and potentially for guiding treatment, yet practical methods for dynamic sampling of this fluid and studies correlating results with clinical outcomes are not available. Such methods could also improve our understanding of the mechanisms resulting in long-term sequelae of severe COVID-19.

Multisystem inflammatory syndrome in children/adolescence
Multisystem inflammatory syndrome in children/adolescence (MIS-C/A) is a rare complication seen in children and adolescents who present with a hyperinflammatory syndrome at 4–6 weeks after SARS-CoV-2 infection (see Bogunovic and Merad, 2021 in this issue for a complete discussion). Early biomarkers that predict MIS-C/A are needed to protect children from this rare yet devastating outcome of SARS-CoV-2 infection.
Relapsing disease in highly immunosuppressed hosts

Another troubling phenomenon is seen in highly immunosuppressed patients who are unable to develop adequate antibody responses to SARS-CoV-2, often due to use of B cell targeted therapies. These patients can have relapsing disease with ongoing viral replication, persistent symptoms, and ongoing risk of severe COVID-19, even months after initial infection. These patients are currently being treated with repeated courses of antivirals and/or convalescent plasma or mAbs. Understanding correlates of natural protective immunity and developing assays to identify those who are at risk for relapsing infection is of great interest.

Multi-system inflammatory sequela within long COVID syndromes

One of the key distinctions in disease caused by SARS-CoV-2 compared with other respiratory infections is the persistence of symptoms in a large proportion of COVID-19 patients. In some hospitalized COVID-19 patient cohorts, over 60% have reported persistent symptoms after discharge. Long COVID syndromes are usually defined by symptoms lasting more than 12 weeks, well after the acute illness has resolved. Though common in patients who were hospitalized, long COVID syndromes are thought to be distinct from post-hospital or post-intensive care unit (ICU) syndromes, and there are numerous cohort studies documenting a variety of long-term symptoms that can affect all the organ systems of the body.

Not surprisingly, persistent pulmonary, cardiac, and renal effects are often related to the severity of the initial illness. These symptoms are present more often in people who spent prolonged periods in the ICU with ARDS but are not limited to this group. Pulmonary effects include ongoing dyspnea with exertion, manifested by diminished results on 6-min walk tests and reduced diffusion capacity on pulmonary function testing. When high-resolution chest computed tomography is performed 3–6 months after hospital discharge, the degree of lung fibrosis and interstitial thickening seen correlates with the initial severity of infection. Cardiac symptoms include chest pains and palpitations, associated with myocardial inflammation on magnetic resonance imaging (MRI). Chronic renal dysfunction is observed in some patients who had acute kidney injury during the initial infection. Thromboembolic events such as deep venous thrombosis and stroke can occur after 4 weeks but are rarely seen after 12 weeks. Gastrointestinal symptoms include bloating, dyspepsia, and other symptoms related to irritable bowel syndrome, possibly due to long-term changes in the gut microbiome. Endocrine manifestations have included new onset diabetes and thyroiditis, possibly due to autoimmune mechanisms. New onset of systemic rheumatologic diseases has additionally been reported, such as giant cell arthritis, dermatomyositis, and inflammatory arthritis within weeks of SARS-CoV-2 infection. This raises the important question as to whether COVID-19 can trigger rheumatologic disease or accelerate subclinical autoimmune processes.

The most frequent long-term effects appear to be neurocognitive and psychiatric. These symptoms are not related to the severity of initial infection and are often seen in people who were never hospitalized for COVID-19. The most commonly reported symptoms associated with a long COVID syndromes are severe fatigue and headache. A major concern is cognitive dysfunction, referred to as “brain fog” by patients, with inability to focus, trouble with memory, attention, and word-finding. The severe fatigue and post-exertional malaise interferes with the ability to perform work at the same levels as before the acute illness. There appears to be overlap in many of these symptoms with myalgic encephalitis/chronic fatigue syndrome (ME/CFS). Patients also present with postural orthostatic tachycardia syndrome (POTS), which is thought to reflect autonomic disturbance, which is also associated with ME/CFS. Both long COVID syndromes and ME/CFS may reflect a neuroinflammatory state. The immunologic pathophysiology is being actively studied in both settings, and findings may help define common treatments for both conditions. Along with standardized neurocognitive testing, understanding correlate biomarkers will be critical for prevention and treatment of the neuropsychiatric outcomes of long COVID syndromes.

A pathological inflammatory response to SARS-CoV-2 infection

In line with a hyperinflammation-driven damage hypothesis, patients with severe COVID-19 have an increased number of mature and immature granulocytes and monocytes in the blood and a significant reduction of circulating lymphocytes including alpha/beta and gamma/delta T cells and mucosal invariant T cells in addition to reduced dendritic cells. The exact cause of lymphopenia is not known, and studies are in progress to determine whether this is due to cell death, excessive recruitment of circulating lymphocytes to peripheral tissues, or sequestration of lymphocytes in lymphoid organs.

The expansion of circulating mature and immature monocytes and neutrophils is likely driven by the excessive release of innate cytokines such as tumor necrosis factor alpha (TNF-α) and IL-6, levels of which correlate with disease progression and severity (Del Valle et al., 2020). A non-mutually exclusive possibility is that comorbidities that are common in patients with severe COVID-19 may contribute to enhanced myeloid cell accumulation in tissues. Older age, diabetes, and obesity, which are significantly associated with severe COVID-19, are all conditions that favor chronic inflammation in tissue. Older age, in particular, biases hematopoiesis toward the myeloid lineage, which may contribute to an excessive response in some infections.

In addition to an altered myeloid compartment, it is also possible that pre-existing vascular damage, common in patients with co-morbidities associated with COVID-19, leads to vascular leakage that further enhances immune cell accumulation in tissues, leading to a reinforcing cycle that amplifies vascular damage leading to coagulopathy events that are common in patients with severe disease.

Myeloid cells are central detectors of viral infections and are key actuators of the anti-viral response, including coordinating innate and adaptive responses and homeostatic tissue repair mechanisms. While many cells including epithelial, stromal, and immune cells likely contribute to the excessive release of inflammatory cytokines, monocytes, neutrophils, and macrophages are significant producers of tissue damaging cytokines. Monocytes and macrophages are also enriched in profibrotic genes consistent with fibroblast expansion (Melms et al., 2021), likely contributing to the lung fibrosis observed in severe COVID-19 patients. Several groups have also observed
It is interesting that the only therapies that have shown benefit in severe COVID-19 patients are corticosteroids and more recently cytokine inhibitors, including IL-6 receptor blockade (RECOVERY Collaborative Group, 2021), despite initial failure of IL-6 blockade to show clinical benefit (Rosas et al., 2021). The discrepancy in outcome between these trials may be due to differences in the timing that IL-6 blockade was initiated during the disease course, the heterogeneity of disease pathogenesis, or changes in standard of care, including the use of steroids in the more recent studies. This highlights the importance of large clinical studies that use a patient stratification algorithm based on extensive clinical histories and biological measurements.

Further insights into the pathogenesis of COVID-19 may be obtained from studies of patients who were treated with cytokine blockade for underlying conditions. These studies have revealed that patients on TNF blockade have significantly reduced hospitalization and death, while patients on steroids had worse outcomes (Gianfrancesco et al., 2020). This is in striking contrast to the benefit of the corticosteroid dexamethasone observed in patients with severe disease, which highlights the non-surprising immunological principle that blocking the immune response at the time of acute virus infection is pathogenic, while blocking an inflammatory response later in disease can be beneficial by reducing inflammation-driven tissue damage. Understanding the imbalance in immunity that results in progression to severe disease remains the major focus of immunologists working on COVID-19 pathogenesis.

**What triggers pathogenic inflammation in severe COVID-19?**

While ARDS is a common cause of mortality in many severe respiratory infections, the specific immunologic hits and viral virulence factors that drive progression to ARDS are unique to each pathogen. The clear mortality benefit associated with corticosteroid treatment in severe COVID-19 is unusual among respiratory virus infections. This suggests that specific pathways are at play in the pathogenesis of severe COVID-19 that are not relevant to severe influenza virus (or SARS-CoV or Middle East respiratory syndrome coronavirus) infections, for example, where corticosteroids are not beneficial and may cause harm. Additionally, that different populations progress to severe disease caused by SARS-CoV-2 and influenza viruses clearly demonstrates that distinct mechanisms underlie the vulnerability to these pathogens. This is exemplified by infants and young toddlers who are among those at highest risk during influenza virus infections, yet they rarely mount the inflammatory response that leads to severe disease in SARS-CoV-2 infections.

Clues are emerging about the molecular triggers of the inflammatory response in people who are susceptible to severe COVID-19. Dysregulation in the effector response, as discussed above, is a clear phenotype. In addition to this, cumulative data support a model in which susceptibility also arises from persistent and/or aberrant ligands for sensing SARS-CoV-2 infection (virus/viral antigens or immune complexes) along with dysregulation of the specific sensors/receptors that are designed to recognize the presence of “non-self.”

A role for persistent viral replication or viral antigen load in COVID-19 severity is supported by studies showing that early administration of neutralizing antibodies is protective. Because neutralizing antibodies act by limiting virus replication, this observation points to the persistence of viral antigens due to inadequate early neutralizing antibodies as one trigger of the pathological inflammatory response in those susceptible to severe COVID-19. Delayed CD8 T cell and IFN responses, as discussed above, also likely contribute to persistence of viral antigens that can drive disease progression. Indeed, SARS-CoV-2 infections are unusual in that the viral ligands (RNA and/or proteins) can persist in tissues for at least several weeks (Gaebler et al., 2020).

While viral ligands can trigger detection directly through pattern recognition receptors, innate effector cells can also detect viruses by the presence of immune complexes that are formed when antibodies bind to viral particles or viral antigens. These complexes act as a separate type of ligand which triggers recognition of “non-self” through Fc receptors (FcRs). FcRs detect antibodies in multivalent complexes through their Fc domains; because immune complexes are not present in the absence of exogenous
antigens (except in autoimmunity), their detection by FcRs triggers immune activation or modulation that is designed to protect and repair the host. In health, immune complexes are rapidly cleared after detection. This is a critical mechanism for preventing damaging inflammation in settings where antibody-antigen complexes are constantly formed due to chronic infection or autoantibody production. This homeostatic process likely prevents disease in healthy individuals in whom autoantibodies are detected and is central in the clearance and resolution of infections. Dysregulation of this response leads to immune-complex mediated sequelae.

Related to a potential role for immune complexes in triggering the pathologic inflammatory response in severe COVID-19, we and others have recently identified a specific post-translational modification (PTM) of the immunoglobulin G (IgG) Fc domain that is elevated in people with severe COVID-19 (Chakraborty et al., 2020, 2021). This PTM is characterized by absence of core fucose residues (afucosylation) on the N-linked biantennary glycans present on the IgG1 Fc. Afucosylation of the IgG1 Fc increases its affinity for the FcR CD16a/FCγRIIIa, found on immune cells including subsets of NK cells, monocytes, and macrophages (including alveolar macrophages). That afucosylated IgGs are present in patients with more severe COVID-19 may indicate that they have a role in triggering the detrimental inflammatory response. In line with this hypothesis, we have found that patients with mild COVID-19 who later progressed to more severe symptoms had elevated anti-SARS-CoV2 Fc afucosylation together with low early neutralizing antibodies as an antecedent to disease progression. This combination of early non-neutralizing and afucosylated anti-SARS-CoV-2 IgGs predicted disease progression. In further experiments, afucosylated immune complexes triggered release of cytokines such as IL-6 and TNF by primary monocytes in vitro and in the bronchoalveolar fluid of mice in vivo, along with eliciting mononcytic and neutrophil infiltration into the lungs in vivo (Chakraborty et al., 2021).

Why some people produce higher levels of afucosylated IgG antibodies remains unknown. Our prior work has established that this modification is also enriched in patients with severe dengue infections and suggests that some individuals respond to dengue or SARS-CoV-2 infections by producing elevated levels of this Fc glycoform, while others have higher levels of Fc afucosylation at baseline. In addition to afucosylated antibodies, abundant autoantibodies have been found in some patients with severe COVID-19. Most autoantibodies that have been identified reacted with connective tissue antigens, cytokines/chemokines (including IFN-1, discussed above), or additional cell surface proteins, and they can be functional in vitro and exacerbate SARS-CoV-2 infections in vivo (Wang et al., 2021). Whether autoantibody production in COVID-19 is a function of molecular mimicry or as a result of non-specific B cell activation in the context of loss of tolerance is not yet known.

Related to dysregulation of virus sensing in susceptible populations, we have also found that patients with mild COVID-19 who progressed to more severe symptoms had enhanced CD16 expression levels on CD16+ monocytes over patients whose disease resolved. As CD16a is the receptor for afucosylated immune complexes, this finding showed that both the ligand and the cognate receptor in the CD16/antibody signaling axis were distinct in people who ultimately progressed to more severe COVID-19, implicating early dysregulation of this pathway in the abnormal inflammatory response (Chakraborty et al., 2021). If non-neutralizing, afucosylated immune complexes contribute to the overwhelming inflammatory response in some patients with severe COVID-19, we hypothesize that there may be a concomitant defect in host cell phagocytosis/immune complex clearance mechanisms that contributes to the pathogenic response.

Separate mechanisms of dysregulated virus sensing in severe COVID-19 have also been hypothesized. For example, increased TLR/MyD88 signaling was associated with severe disease in a recent study that identified the TLR2 pathway as being central in the inflammatory response to SARS-CoV-2. Interestingly, this work also identified the envelope protein as the TLR2 receptor ligand (Zheng et al., 2021).

Conclusion
It is now established that SARS-CoV2 vaccines largely protect from severe COVID-19, yet individuals who are immunocompromised and/or fail to mount a durable, protective response after vaccination remain at risk of developing severe COVID-19. In addition, most of the world remains unvaccinated. Adoptive transfer of anti-SARS-CoV2 mAbs, where available, will likely be of great benefit for preventing disease progression in patients without adequate pre-existing immunity when delivered early during infection. Of note, anti-SARS-CoV-2 mAbs for passive transfer have increased protective potency when engineered for higher affinity to activating FcγRs, underscoring the interplay between antibody Fab and Fc domain functions (Ravetch et al., 2021). These Fc-engineered SARS-CoV-2 mAbs are entirely distinct in their mechanism of action from the polyclonal, non-neutralizing, afucosylated, anti-SARS-CoV-2 antibodies that may play a role in triggering inflammation. If afucosylated immune complexes can trigger progression to severe COVID-19, this is likely in the context of additional aberrant host responses related to pathogen sensing and/or the effector response (Chakraborty et al., 2020, 2021; Del Valle et al., 2020).

Understanding the mechanisms that drive progression to severe COVID-19 and how to best promote tissue repair will be critical for improving clinical outcomes for patients with this disease. Our hope is that the extraordinary research efforts and funding resources that were unleashed to understand the pathophysiology of COVID-19 can now be harnessed to define molecular pathways that lead to aberrant inflammation and ARDS, the cause of most mortality in COVID-19. Defining mechanisms to block progression to ARDS after SARS-CoV-2 infection remains a major unmet clinical need.

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