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Review Article

On the genetics and immunopathogenesis of COVID-19

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ABSTRACT

Most severe cases with COVID-19, especially those with pulmonary failure, are not a consequence of viral burden and/or failure of the 'adaptive' immune response to subdue the pathogen by utilizing an adequate 'adaptive' immune defense. Rather it is a consequence of immunopathology, resulting from imbalanced innate immune response, which may not be linked to pathogen burden at all. In fact, it might be described as an autoinflammatory disease. The Kawasaki-like disease seen in children with SARS-CoV-2 exposure might be another example of similar mechanism.

1. Introduction

As of now, the spread of the COVID-19 pandemic has not been matched by an effective immune response to curtail the viral infection. Nevertheless, the outbreak has been matched by an outpour of publications in both server and peer-reviewed journals. While it will take quite some time to find a cure for the disease, the time is right now to curate the unprecedented flow of scientific data. In a cursory PubMed search, I came up with 27,746 results for COVID-19 and 14,064 publications that include the nomenclature SARS-CoV-2, which was only coined in February and first published in the beginning of March [1]. Under these circumstances an exhaustive review of the literature would be impractical, or worse, confusing. Rather, I offer a selective analysis of the literature, in the hope of generating some insight—or at least some relevant hypotheses.

2. What is new about the *new* virus?

Not much—the coronaviruses (CoV), identified in the 1960's, is a family of enveloped positive-strand RNA viruses infecting vertebrates [2] that have the largest genomes among all RNA viruses (~30,000 bases) [3]. Their genomes are more than three times as big as those of HIV and hepatitis C, and more than twice influenza's. The E229 and OC43 coronaviruses discovered in 1966, were the first pathogenic CoV that crossed the species barrier and infected humans [4,5] followed by NL63 [6] and HKU1 [7]. As of now, these four endemic human CoV are

responsible for up to 35% of seasonal common colds. Two of them (OC43 and HKU1) came from rodents, and the other two (E229 and NL63) from bats [8]. In 2002, an outbreak of severe acute respiratory syndrome caused by a CoV [9] originated from bats, was retrospectively named SARS-CoV-1. The epidemic ended in July 2003, after intense public health mitigation measures leaving behind a total of 8096 subjects infected and 774 (9.6%) fatalities in over thirty countries. The second major spillover in 2012, Middle East Respiratory Syndrome (MERS) reproduced the severe clinical phenotype of SARS [10]. According to WHO data as of the end of January 2020 there were 2519 confirmed MERS-CoV infections and 866 deaths, a fatality rate of just over 35%. The present outbreak is the third documented spillover of an animal CoV to humans that has resulted in severe disease, to emerge in two decades [11]. However, the current coronavirus-associated acute respiratory disease discovered in December 2019 in Wuhan, China, and named coronavirus disease 19 (COVID-19) became a major global pandemic. As of August 23, there are 23.4 million confirmed cases of SARS-CoV-2 infections globally with 807,134 fatalities due to COVID-19, according to Johns Hopkins University's count.

The three CoV that cause severe disease – SARS-CoV-1 (the cause of SARS), MERS-CoV, and SARS-CoV-2 –all came from bats [12–14]. But experts think there is usually an intermediary, an animal infected by the bats that carries the virus into humans. With SARS, the intermediary is thought to be civet cats, which are sold in live-animal markets in China [13]. The origin of SARS-CoV-2 is still unclear. The virus shares 96% of its genetic material with a CoV found in a bat in a cave in Yunnan,

Abbreviations: CoV, coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19, coronavirus disease 2019; MERS, Middle East Respiratory Syndrome; ACE2, angiotensin converting enzyme 2; ADE, antibody dependent enhancement; ARDS, Acute Respiratory Disease Syndrome; TLR, Toll-like receptor; CRS, Cytokine Release Syndrome; IFN, type I/III interferons; SNP, single nucleotide polymorphism; GWAS, genome wide association study; Ab, antibody; NET, neutrophil extracellular trap

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China [14]. However, the SARS-CoV-2 spike protein's receptor-binding domain (RBD) differs in important ways from Yunnan bat virus, which seems not to infect people. On the other hand, a scaly anteater, the pangolin has a CoV with an RBD almost identical to the human version. But the rest of this pangolin CoV is less than 90% genetically similar to SARS-CoV-2, so researchers suspect the pangolin was not the intermediary. Since it has now become evident that humans can transmit the virus to domestic animals, the prospect of identifying the true intermediary host prior to it spreading to humans to begin with, became much more unlikely. Despite the inability to pinpoint the intermediary, the massive sequencing effort all over the world, unequivocally proves that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus [15].

CoV are also one of the few RNA viruses with a genomic proof-reading mechanism which keeps the virus from accumulating mutations [16]. This ability might be why common antivirals such as ribavirin, which can impede viruses such as hepatitis C by inducing mutations, have failed to restrain SARS-CoV-2. Influenza mutates three times more often than CoV do, a pace that enables it to evolve quickly and elude vaccines. CoV on the other hand, frequently recombine, swapping chunks of their RNA with other CoV. Typically, such recombinations are not consequential. But when two distant CoV end up in the same cell, recombination can lead to formidable versions that infect new cell types and jump to other species. This is how experts believe SARS-CoV-2 emerged.

Like most other pathogenic viruses, SARS-CoV-2 interaction with its host follows a life cycle that include receptor binding, membrane fusion, and penetration into the nucleus for replication. Our concept of infectious disease has not changed much in the last 100 years. This is how Ludwik Fleck, an early generation microbiologist and immunologist writes in the 1930's:

“The concept of infectious disease is based on the notion of the organism as a closed unit and of hostile causative agents invading it. The causative agent produces a bad effect (attack). The organism responds with a reaction (defense). This results in a conflict, which is taken to be the essence of disease. The whole of immunology is penetrated with such primitive images of war...It is very doubtful whether an invasion in the old sense is possible, involving as it does interference by completely foreign organisms in natural conditions. *A complete foreign organism could find no receptors capable of reaction and thus could not generate a biological process*” [17] (emphasis added).

Of the seven known pathogenic CoV, three—NL63-CoV, SARS-CoV-1 and SARS-CoV-2 use the same human angiotensin-converting enzyme 2 (ACE2) as cell attachment and entry receptor [18–20]. In all of these CoV the spike glycoprotein (S protein) on the virion surface mediates receptor recognition and membrane fusion. During viral infection, the trimeric S protein is cleaved into S1 and S2 subunits and S1 subunit contains the RBD, which directly binds to the peptidase domain (PD) of ACE2 molecule, while S2 is responsible for membrane fusion. When S1 binds to the host receptor ACE2, another cleavage site on S2 is exposed and is cleaved by host proteases (mainly by TMPRSS2 and Cathepsin L), a process that is critical for viral entry into target cells. The two most notable genetic features of SARS-CoV-2 that likely contribute to its formidable virulence in humans: (1) an RBD that is optimized for binding to the human ACE2 molecule as the viral receptor and (2) the presence of a polybasic furin cleavage site in the spike protein [21]. The RBD of SARS-CoV-2 is ~10-to 20-fold more effective in binding ACE2 than is SARS-CoV-1 [22]. Furthermore, SARS-CoV-2 makes use of the host enzyme furin to cleave the viral spike protein. Furin is abundant in the respiratory tract and found throughout the body. However, hijacking furin is not unique to SARS-CoV-2. It is used by other formidable viruses, including HIV, influenza, dengue, and Ebola to enter cells [23]. By contrast, the cleavage molecules used by SARS-CoV-1 are much less common and not as effective.

Table 1

Comparison of transmissibility expressed as reproduction number, R_0 and case fatality rates of selected human viral diseases. Adopted with changes from Wang et al., [26].

Viral disease	Infectivity: R_0^a	Mortality rate %
Avian H7N9 (2013)	< 1	40
Ebola	2	70
H1N1 (2009)	1.5	0.03
HIV	3	80
Measles	15	0.3
MERS-CoV	< 1	35
Rhinovirus	6	< 0.001
SARS-CoV-1	2–3	10
SARS-CoV-2	3	5–7
Smallpox	6	17

^a R_0 value indicates the estimated number of people infected from one contagious person. Mortality rate data estimates shown in % are based on patients not receiving therapy.

Once the SARS-CoV-2's genetic material gets inside the cell, the virus assumes control over the kinase family of enzymes that through the process of phosphorylation act as switches that turn proteins on or off. The result is that the host's molecular machinery is converted to produce new viral particles. In particular, researchers found that a well-studied kinase network known as the p38/MAPK pathway, which is known to trigger the production of inflammation-inducing cytokines, was significantly activated in cells infected by SARS-CoV-2 [24], a finding that appears to be highly relevant to the pathogenesis of COVID-19. Also SARS-CoV-2 activates a kinase called CK2, which stimulates the production of filopodia, tiny tentacle-like protuberances that extend out from the cell's surface and can function as an infective transport system [24]. Other viruses including Ebola, Marburg virus, HIV, HSV-1 and vaccinia are known to give rise to filopodia along which viral progeny exit cells and travel to infect other cells [25].

Table 1 provides a realistic perspective of SARS-CoV-2 infectivity and COVID-19 severity, within the context of other pathogenic human viral diseases. The four CoV that cause common colds easily infect and actively reproduce in the upper respiratory tract, whereas MERS-CoV and SARS-CoV-1 are more successful at infecting cells in the lower respiratory tract. SARS-CoV-2, appears to do both very efficiently. SARS-CoV-2 can shed viral particles from the throat into saliva even before symptoms start, and these can then pass easily from person to person. SARS-CoV-1 is much less effective at making this leap, infecting others only when symptoms are full-blown. SARS-CoV-2's capacity to infect and replicate both in the upper and lower respiratory tract might explain why people infected have such different experiences. The virus can start in the throat or nose, producing a cough, disrupting taste and smell, and then end there. Or it might work its way down to the lungs and debilitate that organ and the entire organism. It is quite likely that once SARS-CoV-2 gets down in the lungs, it is probably just as deadly as SARS-CoV-1.

In sum, the assessment expressed in the general media, but sometimes also in professional literature [26–29] that the virus is entirely “new” and that the immune system is “naive” namely that it is totally inexperienced when it comes to this virus is exaggerated. A more accurate description of this virus would be a reemergence of a known foe that has a somewhat more optimal organization of its resources making it more suitable to become a pandemic pathogen.

3. How do viral and host genetics affect infectivity and virulence?

The genetic sequence diversity of SARS-CoV-2 is low. As a consequence of a massive effort to sequence viral samples obtained from humans infected all around the world, there are now thousands of viral sequences available which permits an unprecedented and detailed analysis of the virus's genetic evolution. During the early phase of the

outbreak in Wuhan two major lineages of SARS-CoV-2, with different exposure histories, were categorized as L (~70% of sequences) and S (~30%) based on two tightly linked single nucleotide polymorphism (SNP)—a synonymous mutation in the *ORF1ab* of the genome, and a non-synonymous S84L amino acid change in *ORF8*. [30]. The S variant was evolutionarily more related to animal CoV. The functional consequences of the S84L mutation are not known. Nevertheless, the two variants exhibited similar virulence and clinical outcome [31].

A mutation in the spike protein—that mediates SARS-CoV-2 entry into host cells and potentially of functional importance—was described by several teams of researchers [32–35]. The D614G mutation at residue 614 of spike (S) protein causes an amino acid change from aspartate to glycine. The mutation that causes the D614G amino change is transmitted as part of a conserved haplotype defined by four SNPs that almost always track together, although they probably arise independently. Beside the D614G mutation the haplotype includes another nonsynonymous mutation (P322L) in the Nsp12 viral protein. While the functional consequences of the P322L mutation remain unclear at present, there is strong evidence that the G614 variant is associated with greater infectivity and higher viral loads in the upper airways during infection [29,32–35]. The S protein must be cleaved by host proteases to enable membrane fusion, which is critical for viral entry. The G614 mutation creates a novel serine protease cleavage site that can facilitate its cleavage by host serine protease elastase-2 [32]. Also G614 mutation increases both spike stability and membrane incorporation [33]. In cell culture, S-G614 pseudovirus infected ACE2-expressing cells significantly more efficiently than the S-D614 pseudovirus [29,34]. Even though the G614 variant appears to be more infectious, it did not appear to be more virulent since hospital outcomes were similar with either variant [29,33].

Dynamic tracking of variant frequencies sampled from COVID-19 patients from Asia, Europe, North America, and Australia show that the D614 variant was initially dominant, so most subjects infected during December 2019 through the end of February 2020, had this variant [29]. The earliest viral sequence that carried the G614 mutation with the other three SNPs that characterize the haplotype was sampled in Northern Italy on February 20th. During March 2020 both variants could be identified circulating in the population [29,34]. By April, the G614 variant was circulating almost exclusively in European and in the greater NYC area. This variant continued increasing in frequency over several months so that by June 2020 it has become the dominant variant all over the globe. It is tempting to hypothesize that the successful mitigation of the outbreak in China and several other East Asian countries was due, at least in part, to the fact that they faced the less infective D614 variant. The European countries and NYC had to deal with the more infectious G614 variant. Similarly, the early outbreak in Washington State was caused by the D614 variant [34]. The original March-April outbreak on the Western Coast of the United States might have been less severe than in the Northeastern United States, because it originated from the Washington State D614 variant. By June 2020, the G614 became the global dominant variant, and is responsible for the much more infective July phase of the outbreak in the Southern and Western USA. The viral genetic data presented clearly demonstrate that variants may arise quickly, even in CoV, and have profound effects on the spread and consequences of the COVID-19 pandemic.

Prior research has uncovered gene variants that can alter a person's chances of contracting a viral infectious disease. The most famous example is a mutation in the CCR5 gene, which offers protection against HIV. While there are 32 coding variants in human ACE2, with some of them in residues considered important for the binding of S-protein in CoV [36], there is no evidence for the existence of CoV S-protein-resistant ACE2 mutation in any population [37]. Neither is there any evidence for ACE2 variants that bind more, or less, efficiently to SARS-CoV-2 S-protein.

Based on publicly available data from East Asia, Europe and North America, a group of British epidemiologists conclude that children are

half as likely to be infected by SARS-CoV-2 as adults [38]. The reliability of these estimates are limited by lack of direct assessments of the transmission of the virus between adult to child, and child to child, compared with adult to adult. Furthermore, because children tend to have less comorbidities than adults, they experience less disease symptoms, and as such are tested less than adults. Hence, the number of children infected may be grossly undercounted.

A publication that in this short timeframe has already been cited frequently, seeks to confirm that the incidence of SARS-CoV-2 infection is lower in children than adults due to a lower density of ACE2 receptors in the nasal epithelium of children as compared to adults [39]. The researchers report finding less ACE2 RNA in cells scraped from the noses of children than in those from adults. The significant difference in this study is reported to be between those under 17, and those aged 18–60. In addition, there was no difference in the amount of ACE2 RNA detected according to gender, or those with or without asthma. Several caveats to consider: The average relative amount of RNA ranged from 2.4 for those less than 10 years old, to 3.09 for those 25 and older. The differences are relatively small and the error bars large. While those over 60 are those most affected by COVID-19, the study did not include individuals older than 60 years. Also, the density of ACE2 receptors may not be uniform throughout the nasal mucosa, and no evidence is presented that the entire nasal mucosa was equally sampled. Lastly, it is unknown how many receptors are needed for the SARS-CoV-2 virus to successfully infect us. In any case, there is no doubt that children of any age can be infected. I am more convinced by the conclusions of Dong et al. [40] that children of all ages are susceptible to infection by SARS-CoV-2 without significant sex differences. Although clinical manifestations of children's COVID-19 cases seem generally less severe than those of adult patients, young children, particularly infants, are vulnerable to infection.

As the aforementioned publication [39] assumes, if ACE2 is the sole receptor for viral entry, then the expectation is that high ACE2 tissue expression equals higher infectivity and worse outcomes. However, a careful consideration of the role of ACE2 in the renin-angiotensin system pathophysiology is indicative of it playing a protective role—meaning higher ACE2 expression is more likely to protect us from a worse outcome of viral infection. As such, ACE2 has an important role in counterbalancing the effects of ACE1. Angiotensin II, a product of ACE1 cleaving angiotensin I, can cause vasoconstriction, inflammation, and fibrosis. ACE2 cleaves angiotensin II to angiotensin 1–7, which antagonizes the activities of angiotensin II—hence, it can suppress inflammation, fibrosis, and generate vasodilation. Further, a high ACE2/ACE1 ratio protects the integrity of the endothelium and promotes antithrombotic activity. Previous studies have found ACE2 playing a protective role in severe lung injury in ACE2 knockout (KO) mice [41]. ACE2 KO mice challenged with avian influenza H5N1 [42] or H7N9 [43] resulted in severe lung injury, despite that ACE2 is not a receptor for avian influenza. In fact infection with avian influenza strains resulted in downregulation of ACE2 expression in the lung and increased serum angiotensin II, both in mice and human subjects infected by the virus [42].

The question is whether ACE2 expression levels are pertinent to SARS-CoV-2 infection only in the tissues relevant to viral entry and the lungs as its major target, [44,45] or, given that COVID-19 in its severe form is a systemic disease with multi-organ dysfunction [46,47], ACE2 expression levels may be important in multiple organs and tissues other than those of the respiratory system. Relevant to this question, lungs do not have high expression levels of ACE2, and relatively few cell types express ACE2 in the lung compared to other tissues [37,48]. Assuming the importance of ACE2 expression throughout the human organism, in silico analyses have been undertaken through integrating public genomics, epigenomics and transcriptomics data in multiple tissues, different populations, disease conditions, and age as well as sex considerations. Intriguing in silico findings suggest that East Asian populations have higher allele frequencies in expression quantitative

trait loci (eQTL) variants associated with higher ACE2 tissue expression compared to European and African populations [37,48]. Furthermore, ACE2 expression increases by estrogens and to a much lesser degree by androgens, which possibly explains the higher ACE2 expression in females [48]. The study suggests an inverse age-dependent ACE2 expression in both males and females, a reduced expression in type 2 diabetes, and inhibition of ACE2 expression by inflammatory cytokines [48]. These interesting suggestions (supporting a protective role of high ACE2 expression against SARS-CoV2 fatality) need to be validated by clinical observations, in vivo, and in vitro experimentation. Until such time, the functional consequences of ACE2 expression levels to the susceptibility or response to SARS-CoV-2 remain unclear [49].

In addition to ACE2, viral entry requires S-protein cleavage at the S1/S2 and S2' sites allowing fusion of viral and cellular membranes by host proteases. The transmembrane serine protease S2 (TMPRSS2) is frequently employed for this purpose by SARS-CoV-1 and SARS-CoV-2 [20,50], but also by MERS [51], and human CoV-229E [52]. The functional importance of TMPRSS2 in CoV infections was tested in TMPRSS2 KO mice infected with SARS-CoV-1 and MERS-CoV. Results show that lack of TMPRSS2 in the airways reduced severity of lung pathology after infection by SARS-CoV-1 and MERS-CoV, despite that all other host proteases were intact [53]. Apart from CoV, TMPRSS2 is an important host protease for influenza viruses, by cleaving the influenza virus hemagglutinin (HA) molecule [54]. Furthermore, genetic variants with higher TMPRSS2 expression increase susceptibility to severe human H1N1(2009) and avian H7N9 influenza [55]. These findings, raise the intriguing question whether genetic variants with higher TMPRSS2 expression confer higher risk and/or severity of SARS-CoV-2 infections. A preliminary study from Italy suggests that two distinct TMPRSS2 haplotypes show significant frequency differences between Italian and East Asian populations [56]. Specifically, the rare alleles of these haplotypes predicted to induce higher levels of TMPRSS2, are more frequent among Italians. A SNP belonging to one of the haplotypes is the same one found to be associated with increased susceptibility to severe influenza [55].

As will be discussed further, cytokines play an essential role in the pathogenesis of COVID-19. While environment, microbiome, genetics, and host factors, each can influence cytokine responses to pathogen stimulation, genetic variations appears to be a main component shaping cytokine responses in humans [57]. For perspective, the microbiome does seem to have a smaller impact on cytokine production capability. It is estimated that microbiome explain only 10% of cytokine production [58]. Large-scale studies from the Human Functional Genomics Project [57] have shown that different cytokines have different levels of genetic influence. This is an important concept for host defense and disease, as cytokines are fundamental in orchestrating overall immune responses, and can drive pathology when dysregulated, as is the case in COVID-19. Pertinent to the present discussion, the IL-1 β /IL-6 pathway especially, seems to be regulated mainly by genetic factors [57]. My own early work, has provided evidence for the heritability of TNF α production capability in mouse and man [59,60]. Notwithstanding the current paucity of such studies in CoV, I strongly believe this area of research promises to generate valuable information as for the pathogenesis and potential treatment of COVID-19.

African Americans infected with SARS-CoV-2 seem to be at a greater risk for severe outcome. While comorbidities and socioeconomic circumstances certainly play a critical role, cytokines may have an important role too. A preliminary study compared expression levels of cytokines and other immune modulators between Caucasian Americans and African Americans using RNAseq data [61]. Results show IL-1 β and IL-18 receptor 1 (IL18R1), IL12R β 1, TLR7 and TLR9 were significantly higher in African Americans suggesting perhaps the tendency to develop higher inflammatory cytokine responses. Much more work is needed to validate these observations.

Genome wide association studies (GWAS) allowing the unbiased clustering of genetic variation defining human diseases, require

assembly of DNA samples from very large number of subjects which usually take a long time to collect. Given that we are just six months into the pandemic, it is quite remarkable that a medium size GWAS was already completed. It is the first to document a statistically significant association between genetic variants and severe COVID-19 [62]. Variations at two loci in the human genome were associated with an increased risk of respiratory failure in patients with COVID-19; one, within the ABO blood type cluster on chromosome 9, and the other at position 3p21.31. The frequency of the chromosome 3 risk allele was significantly higher in those patients that needed mechanical ventilation, compared to those with less severe disease progress. Importantly, this locus is home to six genes, and it is not yet possible to identify which of them is responsible for aggravating the disease course. This locus contains a cluster of chemokine receptors, XCR1, CCR9 and CXCR6 (and several other cytokine receptor genes close by), which have important regulatory functions in the innate immune system. Another candidate within the locus, SLCA20 is an amino acid (proline) transporter expressed at luminal membrane of small intestine and proximal tubule kidney cells and functions in absorption of proline. Its expression in rodent intestine depends on the presence of ACE2 [63]. However, amino acid transporters have been shown to induce cytokine responses: Genetic variation at the SLC36A4 amino acid transporter show strong association with pathogen induced IL-22 production [57]. Also amino-acids or amino acid catabolites have been reported to modulate cytokine production [64,65]. So it is conceivable that SLCA20 might influence the course of COVID-19 severity by affecting pathogen induced cytokine production, rather than viral entry through ACE2. In this respect, the same risk SNP in the chromosome 9 ABO blood type cluster that affects COVID-19 severity has been associated with elevated IL-6 levels in childhood obesity in a previous GWAS, thus, possibly linking this genetic allele with elevated IL-6 levels (with or without full-blown 'cytokine storm') described in severe COVID-19 patients.

The study [62] is equally striking for the genes that failed to turn up. Pathogen microorganisms, including several viral infections, are controlled by genetic variations at the HLA complex at chromosome 6p21 [66,67]. The class I and class II gene products of the HLA are involved in antigen presentation, a mandatory process to initiate an adaptive immune response geared to restrain a pathogen. But genetic variants at the HLA region did not appear to make a difference in the risk of severe COVID-19. Thus, the so called 'adaptive' arm of the immune system seems to be less relevant to COVID-19 than the 'innate' immune response. I have offered here a hypothesis for what these genetic associations might actually mean. If correct it has major mechanistic implication as for the pathogenesis. At minimum it suggests avenues for further studies.

4. Innate immune response: Friend or foe?

Recognition of a pathogen by the innate immune system triggers the secretion of the crucially important type I/III interferons (IFN). The result of IFN signaling is the activation of an entire cascade of events that include the release of proinflammatory cytokines which further signal to endothelial cells, which then enable chemokines to spread throughout the blood to recruit innate immune cells to the site of infection. The recruited NK cells, monocytes, and neutrophils interact with activated endothelium to leave the blood stream and migrate toward the site of infection. At the site of infection they can perform effector functions to control infections, such as release of reactive oxygen species (ROS) and directly killing infected cells, as well activating a pathogen specific adaptive immune response.

Given the shared sequence homology, the virus-host interactions of SARS-Cov-2 is likely to be analogous to those involving other CoV. However, these interactions might be similar to other non-CoV viruses as well because of limited repertoire and conserved mechanisms of innate immune signaling. SARS-CoV-2 engages host pattern recognition receptors (PRR), and toll-like receptors (TLR) which initiate

downstream signaling pathways triggering secretion of cytokines. If present early and properly localized, IFN are considered the most effective in limiting CoV infections [68]. IFN induced proteins can interfere with viral entry and S-protein-mediated membrane fusion [69,70]. However, in a later phase of the infection, IFN can become pathologic (e.g. upregulation of ACE2 in airway epithelium [45] and orchestration of inflammatory response contributing to immuno-pathogenesis [127]). SARS-CoV-2, similar to other CoV, have developed multifaceted mechanisms to inhibit IFN induction and signaling [71]. This is evident by an early impaired IFN signature in severe COVID-19 patients [72,73], while actively promoting other inflammatory pathways contributing to pathology (e.g. secretion of pro-inflammatory cytokines interleukin (IL) 1 β (IL-1 β) and IL-18 [74]). SARS-CoV-2 is particularly effective in inducing IL-6 and IL-8, by inhibiting an endogenous NF- κ B repressor, NKRFB [75] but probably by other mechanisms as well. While the human innate immune system resources remained unchanged, CoV employ multiple innate immunity evasion mechanisms as reviewed recently [27,76].

The earlier CoV infections can provide an important road map to understand COVID-19 pathogenesis. Thus, a clear indication that immunopathogenesis contributes to SARS was the observation that SARS-CoV-1 viral loads were found to be decreasing while disease severity increased [77,78]. Longitudinal *in vivo* experiments in which ferrets were infected with SARS-CoV-2 intranasally showed a robust production of cytokines that continued beyond clearance of the virus. By day seven, despite waning viral burden, the cytokine response continued to expand. Remarkably, by day fourteen, while the virus was fully cleared, some cytokines and specifically IL-6 remained elevated [73]. In fact, IL-6 emerges as the dominant cytokine driving the immunopathogenesis. Given that old age appears to be an independent risk factor for developing severe COVID-19 [79], it is noteworthy that in a groundbreaking study Ter Horst et al., have shown a clear and consistent increase in IL-6 and IL-1RA production in old age [80].

Evidence is accumulating in COVID-19 patients pointing to dysregulated monocyte driven dendritic cells and macrophage responses, which then drive the characteristic acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS) [81].

CD56^{dim} NK cells, generally thought to contribute to antiviral host defense through cell-mediated cytotoxicity, were depleted primarily in severe cases. Whereas CD56^{bright} NK cells, which are considered producers of IFN- γ and TNF- α , were significantly depleted in all COVID-19 samples tested [82]. Evidence supports recruitment of NK cells from the periphery to the lung. Activation of these NK cells in the target tissue in an environment enriched for IL-6 (and other cytokines) probably contributes to pathogenesis [76,83], as opposed to resolving the infection.

Severe cases of COVID-19 have significant increase in neutrophil levels in circulation [84,85] and in bronchoalveolar lavage fluid (BALF) [86]. Together with the upregulation of chemokines, particularly those that act as chemoattractants for neutrophils and monocytes [73,86–88], these observations support the influx of these cell types into the bronchi. These neutrophils and monocytes probably disrupt the air-blood barrier by causing collateral damage to airway epithelial cells and vascular endothelial cells while increasing cytokine production. The damage to vascular endothelial cells certainly contributes to microthrombosis.

Though seemingly contradictory to mechanisms of immune evasion, enhanced innate immune activation is central to the morbidity and mortality of COVID-19 patients. Immune evasion seems to characterize the first phase of infection with SARS-CoV-2 and this is associated with reduced innate antiviral immunity. However, approximately 20% of infected subjects develop an excessive innate immune activation approximately 7–10 days after infection, which I argue is associated only marginally, if at all, with viral load. Rather, the massive inflammatory response is a consequence of host dysregulation of the immune system. In line with observations in SARS-CoV-1 [89], SARS-CoV-2 induces a robust cytokine response with low levels of IFN in the early phase,

culminating in improper recruitment of inflammatory monocyte-macrophage and neutrophil populations into target organs, resulting in further cytokine production [73].

A recurring theme in COVID-19 pathogenesis is that components of the immune system that are generally thought to contribute to antiviral host defense end up promoting disease severity. Typically, the complement system can efficiently recognize and eliminate viral pathogens by opsonizing viruses and virus infected cells, inducing an antiviral inflammatory state, increasing virus-specific immune responses, and neutralizing cell-free viruses [90]. However, the activation of multiple complement pathways, dysregulated neutrophil responses, endothelial injury, and hypercoagulability appear to be interlinked with SARS-CoV-2 infection and instead serve to drive the severity of the disease [91].

The functional importance of complement activation in CoV was tested in C3 KO mice infected with SARS-CoV-1 [92]. The studies showed that complement activation regulates a systemic pro-inflammatory response and removal of C3 signaling reduced lung injury and respiratory dysfunction, despite equivalent viral loads present in the lungs. This was associated with reduced lung infiltration of neutrophils and monocytes and lower cytokine and chemokine levels in both the lungs and sera [92]. Lung biopsy samples from patients with severe COVID-19 show widespread complement activation characterized by C3a generation and C3-fragment deposition [93].

The host complement activator MASP2, the key serine protease in the lectin pathway of complement activation, was identified as a target of the N (nucleoprotein) protein of SARS-CoV-1, MERS-CoV, and SARS-CoV-2, resulting in aberrant complement activation and aggravated inflammatory lung injury. In mice, lung injury induced by SARS-CoV-1 or MERS-CoV N protein was attenuated when its MASP2-binding motif was altered, when MASP2 was genetically knocked out, or when the MASP2–N protein interaction was pharmacologically blocked [93].

Earlier I have discussed the GWAS that established significant association between severe COVID-19 and the ABO blood type cluster [62]. Having blood type A was linked to an approximately 45% increase in the likelihood that a patient would develop respiratory failure, while subjects with blood group O were at a 35% decreased risk for respiratory failure. A possible mechanistic explanation could be that type O patients harbor both anti-A and anti-B natural IgM Abs. These may help reduce the viral load of their hosts due to early activation of the classical complement pathway followed by viral clearance. Such mechanism has been shown to work *in vitro*, using measles virus produced in cells engineered to express only A-type, B-type or O-type carbohydrate epitopes. Measles virus was neutralized by human serum (that did not contain anti-measles Ab), utilizing natural Abs against the A and B antigens in a strictly complement-dependent manner [94]. These observations support a role for the complement system in enabling natural ABO group Abs as first line innate immune defense to viral infections.

Although most early studies concentrated on the lungs as the target organ in SARS-CoV-2 infection, it is now clear that COVID-19 has a wider spectrum of organ involvement. This may be a result of the broad organ tropism of SARS-CoV-2, but is more likely due to an out-of-control host immune response to the virus. Indeed, evidence is accumulating in support of vascular cell dysfunction in multiple organs during SARS-CoV-2 infection [95]. First, SARS-CoV-2 is able to directly infect engineered human blood vessel organoids [96]. More importantly, histopathological evidence of vasculitis, sometime associated with viral particles, and accumulation of neutrophils and monocytes, and even lymphocytes, in the wall of blood vessels in multiple organs were described [97]. In addition, endothelial apoptosis and pyroptosis might contribute to endothelial cell injury. Similarly, Bryce et al., found diffuse vascular endothelial inflammation with micro and macro vascular thrombosis in the venous and arterial circulation [98]. The vascular endothelium is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis. Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium toward more vasoconstriction with subsequent

organ ischemia, inflammation with associated tissue edema, and a pro-coagulant state [99]. Vascular endothelial damage could explain why people with pre-existing conditions like hypertension, diabetes, obesity, and cardiovascular disease are at a higher risk for severe complications. All of those conditions, identified as independent COVID-19 risk factors, cause endothelial cell dysfunction. The additional damage and inflammation in the blood vessels caused by the viral infection could push them over the edge and cause catastrophic complications [79].

Given that vascular endothelial cells express ACE2, one likely hypothesis suggests that SARS-CoV-2 infects endothelial cells directly which induces injury, activates complement, and sets up a perpetual inflammatory state [91]. However, there are alternative mechanisms for activation of endothelial cells and vasculitis induction that do not necessarily require the presence of the virus itself, e.g. neutrophil extracellular traps (NETs) [100] and hypoxia [101]. The ability of neutrophils to form NETs is considered beneficial in host defense against pathogens, but as observed regarding other innate immune mechanisms, sustained NET formation can trigger a cascade of damaging inflammatory reaction. Indeed elevated levels of NET-specific markers, myeloperoxidase DNA, and citrullinated histone H3, were observed in the sera of COVID-19 patients [102]. As such, several research groups are supporting a more central role for NETs in COVID-19 pathogenesis [102,103].

Coagulation disorders in patients with COVID-19 were initially thought to be due to systemic disseminated intravascular coagulopathy (DIC). However, considerable cross-talk and mutual engagement between the complement and the coagulation cascades is being increasingly documented in COVID-19 and seems to be responsible for a pro-thrombotic environment distinct from DIC, leading to serious adverse outcomes [91,104]. In fact, elevated D-dimer (a fibrin degradation product indicative of hyperactive coagulation) has emerged as a reliable marker of severe COVID-19 [105,106].

Interestingly, the interconnected complement and coagulation cascades, which are being increasingly documented in COVID-19, has been long recognized in antiphospholipid syndrome (APS) [107]. Given that several publications report antiphospholipid antibodies in patients with COVID-19 [108–110], despite them not fulfilling the Sydney criteria for APS [111], it is difficult to ignore how much the clinical and immunopathological picture of APS resembles that of the autopsy findings of an exaggerated inflammatory state and thrombosis in many COVID-19 patients [112,113].

A study by Nicolai et al., provides mechanistic evidence that multisystem disease in severe COVID-19 involves coagulopathy driven by dysregulated innate immune response [114]. They show inflammatory microvascular thrombi containing platelets, fibrin, and a large number of neutrophils in the lung, kidney and heart. Neutrophils were highly activated in severe cases compared to less severe cases and platelets showed enhanced neutrophil adhesion and NET formation in multiple organs. Thus, dysregulated immunothrombosis is linked to both ARDS and systemic hypercoagulability [114].

In sum, an overwhelmed innate immune system is seemingly unable to assemble a balanced response of appropriate cells, cytokines and other molecules to control the infection in a timely fashion. Instead, a disoriented, misguided storm of inflammatory cytokines ends up destroying that which it intended to protect.

5. What happened to the adaptive immune response?

It disintegrated in moderate and severe COVID-19—lymphopenia with drastically reduced CD4+ and CD8+ T-cells is the most consistent finding in moderate and severe COVID-19 patients, which also correlates with disease severity and mortality [115–118]. B-cells are decreased as well [119,120], though the decrease in B cells is not as consistently observed as T cells. Direct infection of T- or B-cells by SARS-CoV-2 has not been reported and is unlikely to be the case [88].

Despite the fact that lymphopenia seems to be a prominent feature

of severe COVID-19, patients under immunosuppressive therapy are not at a higher risk for infection, and if infected seem not to be destined to have more severe progression. In fact, reviewing the mortality and morbidity reports published on SARS-CoV-1, MERS-CoV, and COVID-19, no mention is made on immunosuppression as a risk factor for morbidity and mortality. Further, no severe complications or fatality is reported to be linked to transplantation, chemotherapy, autoimmune hepatitis, IBD, or other conditions requiring immuno-suppressive treatment for patients at any age [121,122]. These observations reinforce the notion that the reduced T and B lymphocytes in COVID-19 patients is not the direct cytopathic effect of the virus itself.

The possibility that the peripheral lymphopenia observed in patients with COVID-19 reflects recruitment of lymphocytes to the respiratory tract or adhesion to inflamed respiratory vascular endothelium has been suggested [31]. Although autopsy studies of patients' lungs and single-cell RNA sequencing of BALF do identify the presence of lymphocytes, the lymphocytic infiltration is modest at best, arguing against sequestration as a main cause of lymphopenia [123].

The most likely scenario is that inflammatory cytokines are key factors behind the observed lymphopenia. Indeed, serum levels of IL-6 especially have been closely correlated with lymphopenia, while recovered patients show return of lymphocytes numbers toward the normal range with significant reduction in IL-6 levels. A likely mechanism is via the downregulation of multiple HLA class II molecules on CD14+ monocytes and B-cells by IL-6, as demonstrated by multiple studies [82,119,120]. HLA class I molecule downregulation was less severe and inconsistently observed. A negative correlation between serum levels of IL-6 and the number of class II HLA on CD14+ monocytes supports the notion of downregulation of class II by IL-6 [82,119]. This decrease in HLA molecules suggests that severe COVID-19 patients might be unable to mount a normal T cell response due to reduced antigen presentation capability to T cell receptors (TCR). Such T cells are then eliminated by apoptosis. Autopsy studies on lymphoid organs collected from patients who succumbed to the disease revealed massive lymphocyte death, which was linked to high levels of IL-6 as well as Fas-induced apoptosis [124]. Treatment with Tocilizumab, an IL-6 receptor antagonist, restores, at least partially, the HLA class II molecules on antigen-presenting cells. In addition, it increased the number of circulatory lymphocytes, further suggesting IL-6 is a key player in the lymphopenia development [119]. Further, NK T-cells are reduced in number and impaired in function in severe COVID-19 in an IL-6 dependent manner [120].

Since CD8+ T cells require antigen presentation by HLA class I for activation via TCR, and these molecules are less reduced than class II molecule, it is unlikely that the same mechanism of apoptosis of inactivated CD4+ T cells would be operating to a similar extent in CD8+ T cells. Rather, it is possible that most CD8+ are eliminated due to activation/exhaustion of T cells [116].

Intense immune profiling of COVID-19 patients show a very heterogeneous immune response. A rigorous comparison between the studies is complicated by major differences in cohort sizes, dissimilar clinical phenotypes used, utilization of different experimental strategies, and emphasis on different parameters by various investigators. The study by Giamarellos-Bourboulis et al. [119] suggest that severe COVID-19 patients developing severe respiratory failure show one of two immune phenotypes: (1) an immune dysregulation phenotype (~75% of patients) characterized by major reduction of HLA-class II molecules on CD14+ monocytes in the absence of elevated ferritin. This is triggered by monocyte hyperactivation, excessive IL-6 production, and profound lymphopenia, but without IL-1 β elevation; and (2) a MAS phenotype (~25%) associated with elevated ferritin, with relatively less reduction of HLA class II molecules on monocytes and triggered by IL-1 β . Further studies will be needed to verify whether these immunophenotypes are generalizable.

Mathew et al. [125] identified a subgroup of approximately 20% of severe COVID-19 patients that lack detectable lymphocyte response to

the infection, suggesting a total failure of immune activation. Further, these investigators emphasize that the typical T-cell/B-cell communication and cooperation, the adaptive immune system depends on, is practically nonexistent in some COVID-19 patients.

Lucas et al., [126] confirmed an overall increase in innate cell lineages, reduction in HLA class II molecules on monocytes, and early surge in cytokines with parallel reduction in T cells, observed by many other studies. In addition, according to these investigators the immune responses to pathogens can be roughly grouped into three categories characterized by different sets of immune cells and cytokine signals used: type 1—broadly T_H1 responses directed against viruses and intracellular bacteria; type 2—directed against parasites that do not invade cells; and type 3—directed against fungi and bacteria that can survive outside the cells. Type 1 immune response expected in SARS-CoV-2 infection was seen in mild to moderate cases, while in severe cases the immune system seemed to invest too many resources in non-appropriate type 2 and type 3 immune signaling. This immune disintegration, the investigators have dubbed as “misfiring,” seems to extend to the realm of T and B lymphocytes [126]. Other investigators describe the catastrophic CoV disease as a lack of switch from an innate immune response to an adaptive immune response [13]. These depictions of the immune response in severe COVID-19 are symbolically captured in Fig. 1.

The antigen specificity of SARS-CoV-2 T cells have just started to be characterized in COVID-19 patients [129,130] and their potential protective role awaits additional research. However, it is already clear that patients who recovered show specificity for multiple SARS-CoV-2 proteins, not only spike protein. Interestingly, cross-reactive memory $CD4+$ and $CD8+$ T cells are also found in ~50% of subjects who have never been exposed to SARS-CoV-1/2 [129,130]. While SARS-CoV-1/2 unexposed donors can recognize both structural and nonstructural viral proteins, nonstructural ORF-1-NSP7/13-specific T cells are often dominant. In contrast, SARS-CoV-1/2 recovered individual preferentially recognize structural proteins [130]. At present no satisfactory explanation for this phenomenon has been offered. Also unclear is how these preexisting memory T cells, which are presumably generated in response to human common cold CoV, affect immunity or pathology upon SARS-CoV-2 infection.

Heterologous viral T cell immunity and immunopathogenesis—an important consideration that has not yet received sufficient consideration in the current viral pandemic, is highly relevant to the observations of cross-reactive T-cell responses in non-exposed subjects. In fact, only laboratory animals kept in pathogen free conditions are naïve. No human more than a few weeks old is immunologically naïve [131]. The

history of previous exposure, not only to related, but also to unrelated microorganisms, can greatly alter the host's immune response to a viral infection and can change the course of disease [131]. In fact, it is very likely that this phenomenon is a common feature of human viral infections. T cells have high levels of cross-reactivity because the TCR first scans the peptide-HLA complex by binding to the HLA, and then it molds itself around the peptide. Actually, the TCR contacts only 2–4 amino acids in the peptide, so the total energy of the TCR-peptide-HLA interaction is heavily influenced by the HLA rather than the peptide. The consequence is a highly promiscuous T cell which allows a large variation in peptide sequences without inhibiting the HLA-peptide-TCR interaction [132]. Hosts that have never experienced a particular virus, might, nevertheless, have memory T cell pools that show specificity for it by virtue of cross-reactivity that can shape the repertoire of the primary response. The observation that the same virus can cause widely different pathological manifestations in humans might be due (at least in part) to an established adaptive immunity toward related or unrelated viruses, which results in enhanced protective immunity in some, reduced protective immunity in others, or altered immunopathology, including enhanced disease severity in some hosts [133].

The role of humoral responses in the pathogenesis of COVID-19 remains unclear. As in SARS-CoV-1 infection, most subjects infected by SARS-CoV-2 seroconvert within 7–14 days after infection and this process is associated with increase in plasma cells, whereas naïve B cells decrease significantly [134]. While recovered patients generate SARS-CoV-2-specific neutralizing Abs and spike-binding Abs currently, their titers are highly variable in different patients [135]. About one third of recovered patients generate very low titers of SARS-CoV-2-specific neutralizing Abs [135,136], and some patients (possibly up to 20%) who recover, do not have detectable neutralizing antibodies at all [129,135,137]. These observations bring up the question of how the virus was cleared—as it eventually was in all those patients studied—without strong Ab responses. We can speculate that T-cell mediated immune responses, or non-specific responses by innate immune cells were responsible for viral clearance. However, since a pathogen that kills off the host that it needs to survive is also threatening its very own existence, the possibility of CoV self-clearing should be considered, especially when alternative hosts are plentiful.

In a remarkable study [137] the levels of total IgG and IgG neutralizing antibodies (as measured using a spike protein pseudotyped virus) were quantified in symptomatic and asymptomatic patients eight weeks after release from the hospital (roughly three months after start of infection). The levels of IgG and neutralizing antibodies were significantly decreased in the majority of patients in both groups. The

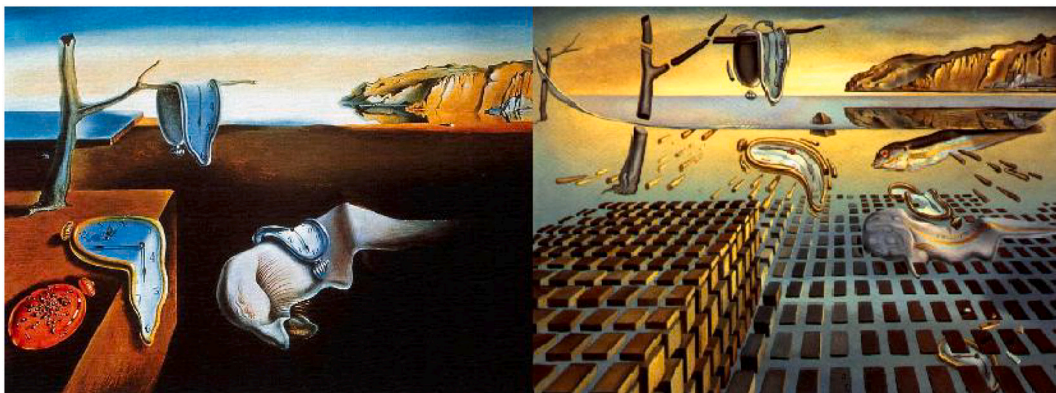


Fig. 1. *The Disintegration of the Persistence of Memory* (1954) (RT) by Salvador Dalí is an oil on canvas reaction to his original work *The Persistence of Memory* (1931). In this version, the landscape from the first painting has been engulfed by water. Disintegration of objects is occurring above and below the water. The block and plane from his original (LT) have now been separated into brick-like objects that float. Some of the bricks on the left side of the painting begin to disintegrate. A watch beneath the water is coming to pieces and another one that sunk beneath the layer of bricks, leaves bits of debris behind. While *Persistence of Memory* (LT) symbolizes the importance of immunological memory as cornerstone of adaptive immunity, the *Disintegration of the Persistence of Memory* (RT) is a metaphor for the adaptive immune response in COVID-19 [128].

decrease in neutralizing Abs was more pronounced in asymptomatic (~80%) as compared to symptomatic (~60%) patients. Taken together, the finding that ~20% of people infected with SARS-CoV-2 do not make anti-viral Abs, added to the observation that neutralizing Abs begin to drop noticeably during convalescence—suggests that infection with SARS-CoV-2 does not establish long-lasting serological immunity, at least not for those who are asymptomatic or mildly ill (more than 80% of all those infected by SARS-CoV-2). Even more problematic—several studies show significantly higher IgG and IgA Ab responses. This does not correlate significantly with protection, but rather with severity of disease [138–141] similar to what was seen in SARS [142]. At minimum, these studies suggest that a robust Ab response is insufficient to protect from severe disease [76].

While it is frequently assumed that anti-SARS-CoV-2 Abs might be either beneficial or irrelevant, there is also the possibility that such Abs might actually be detrimental. First, Abs can cause immunopathology by binding viral fragments followed by activation of the complement cascade by the Ab complex. The consequences of complement activation in the pathogenesis of COVID-19 was discussed above (section 4), and extensively reviewed by others [91]. Second, Ab responses to CoV may contribute to pathology via Ab-dependent enhancement (ADE). ADE is mediated by non-neutralizing virus-specific IgG engagement of Fc-receptors (FcR) expressed on immune cells, particularly monocytes and macrophages, leading to inflammatory activation of these cells. Anti-S-IgG passive immunization of SARS-CoV-1-infected rhesus monkeys significantly enhanced the viral induced acute lung injury with massive accumulation of monocytes and macrophages in the lung in an Fc γ R dependent fashion [143]. Further, serum containing anti-S-IgG from patients with SARS-CoV-1 enhances the infection of SARS-CoV-1 in human monocyte-derived macrophages in vitro [144]. A monoclonal Ab isolated from a patient with MERS, targeting the S-protein of MERS-CoV showed FcR dependent ADH [145]. High dose iv immunoglobulin (IVIg) treatment which has shown some efficacy in CoV including COVID-19 [146], may diminish ADH by blocking FcR mediated activities of monocytes and macrophages. Direct evidence for ADE was not documented in COVID-19 patients so far. However, as argued [147], ADE should be given full consideration in the safety evaluation of emerging candidate vaccines for SARS-CoV-2. Finally, it should be emphasized that at present, neither anti-spike neutralizing Abs nor anti-spike T-cell responses have been established as corollaries of protection.

6. COVID-19—Autoimmune or autoinflammatory disorder?

Patients afflicted with a chronic autoimmune disease have an increased risk of infections including viral infections [148,149]. Likewise, acute viral infections may also exacerbate pre-existing autoimmune disease, and immunosuppressive therapies may render patients with autoimmune disease more vulnerable to viral infections. Despite these compounded considerations, patients with systemic or organ specific autoimmune disease are not at increased risk for infection with SARS-CoV-2. In fact, of the hundreds of reports published, none mention autoimmune conditions as either independent risk factors for disease or as indicative of a more severe outcome if infected. The data actually suggests that the rate of infection with the virus and their clinical course is not any different from that of the general population [150–152]. Those autoimmune afflicted patients that have developed severe COVID-19, are likely to have other comorbidities that are independent risk factors for severe disease. While virus infections can cause flares in otherwise stable autoimmune disease, the data suggests that SARS-CoV-2 infection is not associated with increased incidents of autoimmune flares. I have previously (section 5) discussed and presented evidence that patients under immunosuppressive therapies, including those afflicted with autoimmune conditions are not at increased risk for infection or for more severe outcome [121,122].

Regarding SLE, the prototypic systemic autoimmune disease, a group of investigators suggested that inherent epigenetic dysregulation

causing hypomethylation and overexpression of ACE2, the functional receptor for SARS-CoV-2, might facilitate viral entry, viremia, and increased likelihood of cytokine storm in such patients [153]. The aforementioned role of ACE2 expression, as discussed above, suggests that higher expression of ACE2 might actually benefit the host more than it benefits the virus. In any case, the clinical experience and published data do not support these predictions. Moreover, the accumulating scientific information does not support the notion that severe COVID-19 is a direct cytopathic viral disease, but rather a disease in which multi-organ insult occurs by the host's own immune system [154].

Conditions in which the immune system attacks its own tissues are usually associated with development of autoAbs. Indeed, Gagiannis et al., studied prospectively a group of 22 patients for the possible role of autoimmunity in COVID-19 patients [155]. AutoAb titers $\geq 1:100$ were detected in 10/11 COVID-19 patients who required intensive care treatment, and in 4/11 patients with milder clinical course. Based on serological, radiological, and histopathological similarities between COVID-19-associated ARDS and acute exacerbation of connective tissue disease induced interstitial lung disease, these authors suggest that SARS-CoV-2 infection might trigger or simulate a form of organ specific autoimmunity [155]. Similarly, Zhou et al., report on autoAbs in 21 severe COVID-19 patients. The prevalence of anti-52 kDa SSA/Ro Ab, anti-60 kDa SSA/Ro Ab, and antinuclear Ab (ANA) was 20%, 25%, and 50%, respectively [108]. ANA was reported in over 35% of 45 consecutive COVID-19 patients [110].

Several studies document different aPL Abs in COVID-19 patients mostly associated with thrombotic phenomena [108–110,156,157]. Whether aPL in COVID-19 is transient, as has been documented in many other viral infections, or develops into persistent and pathogenic, is very difficult to judge from the results published so far. Pregnancy related morbidity with fetal losses have not been reported in connection with SARS-CoV-2 infections. However, since an infection often precedes the clinical onset of APS, it is certainly justified to follow up a positive aPL test in a COVID-19 patient with a repeated test approximately twelve weeks later to further evaluate the possibility of post-infectious APS.

A Kawasaki-like disease seen in children is the closest link between SARS-CoV-2 and the appearance of an autoimmune and/or autoinflammatory condition. Investigators from Italy's pandemic epicenter in Bergamo were the first to focus attention on this disorder [158]. D'Antiga and his colleagues, quantified the time course and incidence of Kawasaki-like disease in children before and after the COVID-19 pandemic, documenting a thirty-fold increase in incidence of Kawasaki-like disease after the beginning of the pandemic [158]. Kawasaki disease is an acute and usually self-limiting vasculitis of medium and small sized arteries with specific predilection for the coronary arteries that affects previously healthy young children typically under the age of five years. In the acute phase of the disease, patients with Kawasaki disease might have hemodynamic instability, a condition known as Kawasaki disease shock syndrome. Same patients with Kawasaki disease fulfil the criteria of macrophage activation syndrome (MAS). An association between Kawasaki disease and various viral infections have been suspected, including viruses of the coronavirus family, however a specific infectious trigger has yet to be identified. SARS-CoV-2 should be now added to the list of implicated viruses. The most accepted pathogenetic hypothesis supports an aberrant response of the immune system to one or more unidentified pathogens in genetically predisposed subjects.

Following the report from Bergamo further reports of similar cases from many countries have been published [159–163]. With approximately 1000 Kawasaki-like cases reported, these studies provide a consistent clinical picture: the disease appears 2–4 weeks after an infection with SARS-CoV-2 and most patients have serological evidence of infection; patients are on average older than those with classical Kawasaki disease; patients experience respiratory and gastrointestinal involvement; signs of hemodynamic instability; greater incidence of

myocardial injury; and more intense inflammatory response due to dysregulated immune response. The incidence of coronary aneurism is lower than in Kawasaki disease, but this may be a consequence of relatively short follow up. Most patients so far have responded well to the same therapies used for classical Kawasaki disease. All these results and considerations support the notion that the immune response to SARS-CoV-2 is responsible for this Kawasaki-like disease [158,163] in susceptible patients.

U.K. pediatricians and their National Health Service defined and named the ‘new’, disease “pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),” or PIMS-TS [159]. The CDC in the U.S. and the WHO subsequently published their own differing definitions of the disorder, which they termed multisystem inflammatory syndrome in children (MIS-C) [160–163]. Physicians and scientists in the field of biology are prone to giving names that are often more confusing than helpful. I have worked for some years on a cytokine named tumor necrosis factor (TNF) that had practically nothing to do with necrosis of tumors, and from any sensible perspective is as much an interleukin (IL) as any of the approximately 50 ILs.

I am not aware of any clinical, therapeutic, or long term follow up consideration that would benefit from a more nuanced definition and naming such as PIMS-TS or MIS-C, rather than simply Kawasaki-like disease. In fact some authors agree that “until more is known about long-term cardiac sequelae of MIS-C, providers should consider following Kawasaki disease guidelines for follow up” [161]. Until a much better understanding of the pathogenesis of Kawasaki disease and Kawasaki-like disease emerges, I do not see a reason to further confuse the literature.

7. Final remarks

As I am writing this essay, the pandemic seems far from being over. It surely looks like we are not even in the end of the beginning. The long-term impact of COVID-19 is too early to evaluate. Patients who have recovered from the disease report lingering chronic fatigue, muscle weakness, loss of sense of smell, and difficulties in concentration. But this might be just the tip of the iceberg. We already know that impaired liver function continues for some time after patients have apparently recovered and the virus has cleared. It is also probable that some patients will have lasting pulmonary damage due to fibrosis as has been documented in about 25% of patients recovered from SARS [164]. Similarly, myocardial scarring will cause cardiac impairment in certain COVID-19 recovered patients. Moreover, the long-term consequences of the massive inflammatory response affecting many tissues, and its effect on the competence of the immune system itself, are unknown. It is, however, possible that the intense inflammation in many tissues might cause cellular damage and exposure of self-antigens eliciting auto-reactive T and B cells and generating an autoimmune disease.

Another question that could take years to answer is whether the SARS-CoV-2 virus may lie dormant in the human body for years and then launch itself later in a different form. For example, after a chicken pox infection, the herpes virus that caused the illness reemerges after decades in form of shingles. Similarly the hepatitis B virus causes the appearance of liver cancer years later.

A general comment is pertinent at this point: the culmination of an interaction between an infectious agent and the human host, even when “full recovery” ensues, does not mean the organism is restored to its previous state (before the encounter), but rather the organism acquires a new equilibrium. As the French physician and philosopher George Canguilhem wrote some 75 years ago:

“contrary to orthodox medical teaching, health is not some absolute state of perfect physical and mental wellbeing. It is the margin of tolerance for the inconsistencies of the environment... Disease is not simply disequilibrium or discordance; it is an effort on the part of

nature to effect a new equilibrium in man” [165].

We have learned a tremendous amount about SARS-CoV-2 and COVID-19 in a short amount of time. The efficient transmission of data exhibited during this time, has been surpassed only by the efficient transmission of the virus itself. Although originally conceptualized as a primarily respiratory viral disease, COVID-19 is now clearly recognized as a far more complex, multi-organ, and heterogeneous illness.

As with SARS-CoV-1 and MERS-CoV, the important considerations for the delicate balance of the viral-host interaction that are responsible for COVID-19 are now increasingly appreciated: (1) fast and robust initial viral replication; (2) early viral inhibition of IFN induction and signaling causing a delayed IFN expression which drives immunopathology; (3) out of balance antiviral innate immune response becomes immunopathogenic; and lastly (4) disintegration of the adaptive immune response. Paul Ehrlich's prediction of horror auto-toxicus—at the turn of the 20th century—has been realized by the innate immune response to CoV in the 21st century.

The language of immunology is rife with war metaphors. For over a hundred years we have been educated to believe in the metaphor that the immune system acts as an army defending our bodies. As Richard Lewontin has written:

“While we cannot dispense with metaphors in thinking about nature, there is a great risk of confusing the metaphor with the thing of real interest. We cease to see the world as if it were *like* a machine and take it to *be* a machine. The result is that the properties we ascribe to our object of interest and the questions we ask about it reinforce the original metaphorical image and we miss the aspects of the system that do not fit the metaphorical approximation” [166].

What has SARS-CoV-2 revealed? For me, the answer is our immune response to COVID-19 serves as proof of everything I have long thought was wrong with viewing the (adaptive) immune system as a defense organization:

It reacts too slowly.

It fights today's threats with the solutions of past problems.

It is susceptible to exploitation.

It destroys that which it intended to protect.

It is large, complicated, elaborate and wasteful [167].

If you stand back and evaluate how ineffective is the immune system as a defense organization, it is only logical to conclude that it was never intended as one.

SARS-CoV-2 will eventually be contained, but not by our immune systems. Rather, by the international brotherhood of the scientific community. Epidemics have always played a natural part in the fabric of human history, but there has never been a time in history where so many different and powerful tools were available to accomplish this task. Of all human conditions that disseminate virulent diseases, hubris emerges across centuries as a key driving force. We should embrace Cesar Augustus motto “Festina lente”, make haste, slowly—even or especially when you are feeling the crunch, take your time. This is not the time for us to skip corners.

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