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Comparing the Cytokine Storms of COVID-19 and Pandemic Influenza

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Emerging respiratory viruses are major health threats due to their potential to cause massive outbreaks. Over the past 2 years, the coronavirus disease 2019 (COVID-19) pandemic has caused millions of cases of severe infection and deaths worldwide. Although natural and vaccine-induced protective immune mechanisms against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been increasingly identified, the factors that determine morbimortality are less clear. Comparing the immune signatures of COVID-19 and other severe respiratory infections such as the pandemic influenza might help dissipate current controversies about the origin of their severe manifestations. As such, identifying homologies in the immunopathology of both diseases could provide targets for immunotherapy directed to block shared pathogenic mechanisms. Meanwhile, finding unique characteristics that differentiate each infection could shed light on specific immune alterations exploitable for diagnostic and individualized therapeutics for each case. In this study, we summarize immunopathological aspects of COVID-19 and pandemic influenza from the perspective of cytokine storms as the driving force underlying morbidity. Thereby, we analyze similarities and differences in the cytokine profiles of both infections, aiming to bring forward those molecules more attractive for translational medicine and drug development.

Keywords: COVID-19, SARS-CoV-2, influenza, flu, cytokine storm, cytokines

Introduction

Outbreaks of viral pneumonia have occurred all along human history. Although the mechanism behind morbidity remained unclear for decades, current paradigms indicate that besides the microorganisms' virulence, an overdriven host immune response mediates devastating manifestations of infections. This idea has gained further notoriety after the coronavirus disease 2019 (COVID-19) pandemic. Thus, it is now accepted that the critical forms of the disease are frequently accompanied by excessive cytokine release into the circulation (hypercytokinemia) (Mehta and others 2020).

Despite advances in understanding COVID-19 pathobiology, the exact cytokine networks involved in severe manifestations and how each factor contributes to lung damage are unclear. Defining immune profiles associated with morbidity is complex due to the impact of genetic and comorbidity differences across populations. In this scenario, lessons from other respiratory infections might aid dissipating uncertainty about COVID-19 immunopathology. Influenza viruses are the prototype airborne pathogens leading to periodic epidemics of variable severity, the last occurring in 2009 after the appearance of a novel A (H1N1) subtype (Centers for Disease and Prevention 2009; Novel Swine-Origin Influenza and others 2009; Perez-Padilla and others

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2009). Similar to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pandemic influenza A (H1N1), hereinafter referred to as influenza, is characterized by a broad clinical spectrum encompassing critical respiratory illness with hypercytokinemia (Liu and others 2016; Thomas and others 2017).

This review compares cytokine storm syndromes (CSS) observed during COVID-19 and influenza to detect conserved immunopathogenic mechanisms underlying severe disease. Moreover, by highlighting unique immune profiles in critical COVID-19, we provide the theoretical bases for future research on specific cytokine networks implicated in pathogenesis that could be targeted through immunotherapy.

Infectious CSS

Mechanisms

Cytokines coordinate the immune response activation, regulation, and amplification. They have short half-life times, and their production is very regulated to prevent systemic damage (Cavaillon and others 1992). Cytokines act through common intracellular pathways to control intercellular interaction and communication, and they have autocrine, paracrine, or endocrine effects (Zhang and An 2007). Once released, cytokines induce the production of more cytokines (cytokine cascades). A cytokine storm (CS) is an increase in circulating cytokines causing acute systemic symptoms and organ dysfunction (Fajgenbaum and June 2020). The term was first used for graft-versus-host disease in 1993 (Ferrara and others 1993). Nevertheless, this phenomenon was associated with infections until the H5N1 influenza virus emergence in 2005 (Yuen and Wong 2005).

It is well known that CSS can occur in various contexts due to excessive cytokine production or inadequate anti-inflammatory responses. For instance, the hemophagocytic syndrome (HPS), also named hemophagocytic lymphohistiocytosis (HLH), is characterized by immune overstimulation. This condition can be primary and secondary according to its cause (Buyse and others 2010; Canna and Behrens 2012). Primary HLH, as in the case of familial HLH, derives from genetic mutations altering the function of natural killer (NK) cells and cytotoxic T cells (Stepp and others 1999). However, it also includes other inherited immunodeficiencies, such as the Chédiak–Higashi syndrome, Griscelli syndrome, and type II Hermansky–Pudlak syndrome (Emmenegger and others 2005). The typical cause of secondary HPS is infections, especially related to the Epstein–Barr virus, human immunodeficiency virus, herpesvirus 1, bacteria, and fungi.

Nonetheless, it can also be associated with autoimmune diseases and malignancies such as leukemia and lymphoma (Al-Samkari and Berliner 2018). Macrophage activation syndrome is also a secondary HPS associated with rheumatic diseases, especially systemic juvenile idiopathic arthritis, systemic lupus erythematosus, and adult-onset Still's disease (Fukaya and others 2008). Also, the cytokine release syndrome is a class of CSS occurring in patients with B cell malignancies after chimeric antigen receptor T cell immunotherapy (Porter and others 2015).

Typical manifestations of hypercytokinemia include fever, malaise, anorexia, hypotension, hypoxia, arthralgia/myalgia, nausea, diarrhea, tachycardia, tachypnea, altered mental status, diffuse lymphadenopathy, hepatosplenomegaly, rash, pulmonary edema, pneumonitis, and renal failure. There are also common laboratory findings characteristic of an acute-phase response such as leukocytosis/leukopenia, thrombocytosis/thrombocytopenia, anemia, increased C-reactive protein (CRP), ferritin and D-dimer levels, prolonged prothrombin time, decreased erythrocyte sedimentation rate, hypertriglyceridemia, and hypoalbuminemia (Fajgenbaum and June 2020; Lukan 2020). All these changes are driven by the biological activities of specific cytokines usually overproduced during a CSS.

Sepsis exemplifies an infectious CSS

Sepsis illustrates the clinical consequences of hypercytokinemia during infections and is an example to understand the pathobiology of CSS (Cohen 2002; Schulte and others 2013). Indeed, influenza and COVID-19 also meet the criteria for sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer and others 2016). Clinical manifestations associated with sepsis resemble other CSS and include an increased respiratory rate, altered mental status, and hypotension. Septic shock is a subset of sepsis, in which underlying circulatory and cellular/metabolic abnormalities are that profound to increase mortality substantially. It is characterized by hypotension refractory to fluid resuscitation and increased serum lactate levels (Singer and others 2016).

Sepsis has been intensively investigated for decades, allowing immunologists to discover fundamental mechanisms of immune activation and regulation (Opal 2011). All responses against infections initiate when the innate immune system detects pathogen-associated molecular patterns (PAMPs) expressed by invading microorganisms using pattern recognition receptors (PRRs) such as the Toll-like receptors (TLRs), NOD-like receptors (NLRs), retinoic-acid-inducible gene 1 (RIG-1), among others (Eisenbarth and Flavell 2009). These receptors initiate signaling pathways that culminate in reactive oxygen species and reactive nitrogen species (ROS and RNS) production, complement activation, phagocytosis, chemotaxis, and cytokine expression, increasing blood supply and leukocyte recruitment to the sites of pathogen exposure (Kumar 2020). Nonetheless, alterations to several mechanisms initially deployed to control the infection mediate overdriven inflammation and tissue injury among septic patients.

Several cytokines listed below are overregulated during sepsis and might play a pathogenic role in this condition.

- Tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β). TNFα is expressed as a membrane-bound heterotrimer and is released after shedding by a disintegrin and metalloproteinase 17 (ADAM17) in macrophages, lymphocytes, and fibroblasts. Meanwhile, IL-1β is secreted by monocytes, macrophages, and dendritic cells (DCs)(Schulte and others 2013). TNFα promotes the differentiation of macrophages (Witsell and Schook 1992), expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 in endothelial cells (Nakae and others 1996), and extravasation of neutrophils into tissues (Schulte and others 2013).

TNFα and IL-1β are relevant in developing systemic inflammation and the accompanying coagulation disorders observed during sepsis (Schouten and others 2008). Also, they amplify the inflammatory cascade by prompting macrophages to secrete more cytokines, lipid mediators, and ROS and RNS (Cohen 2002).

- IL-6 is synthesized by macrophages, DCs, lymphocytes, endothelial cells, fibroblasts, and smooth muscle cells. It increases soluble levels of CRP, complement components, fibrinogen, and ferritin (Schulte and others 2013). Furthermore, IL-6 induces the differentiation of $CD4^+$ T cells into Th17 and $CD8^+$ T cells into cytotoxic T cells (Okada and others 1988; Korn and others 2009). TNFα, IL-1β, and IL-6 are considered endogenous pyrogens since they favor prostaglandin E2 synthesis and fever (Schulte and others 2013).
- CXCL8 (also named IL-8) is found at high concentrations in patients with sepsis (MERA and others 2011; Surbatovic and others 2015). CXCL8 is released by macrophages, neutrophils, eosinophils, T lymphocytes, epithelial cells, and fibroblasts, exerting a chemotactic activity on neutrophils (Bickel 1993). Hence, CXCL8 might be implicated in neutrophil-induced tissue damage, a typical lesion observed during sepsis (Shen and others 2017).
- IL-12 and interferon-gamma (IFNγ). IL-12 and IL-18 act synergistically to elicit the release of IFNγ from type 1 T helper (Th1) cells (Zhang and others 1997), but also NK cells, NKT cells, B cells, DCs, and macrophages (Nakanishi and others 2001; Nakanishi 2018). IFNγ has an important antiviral activity and stimulates M1 macrophages to produce proinflammatory cytokines, improve antigen presentation, and exert bactericidal activity (Luheshi and others 2014). Also, IFNγ antagonizes the anti-inflammatory cytokines TGB-β and IL-10 and causes fever, chills, headache, dizziness, and fatigue (Ulloa and others 1999).
- CCL2, CCL3, and CCL4 (MERA and others 2011). These chemokines attract monocytes and granulocytes to the sites of inflammation (Wolpe and others 1988; Zhang and others 1994; Menten and others 2002). Although their function is required for protective immunity against pathogens, their excessive production might worsen leukocyte recruitment and tissue damage.

Cytokines released during sepsis have profound effects on the microcirculatory system. For instance, impaired red blood cell deformability, increased blood viscosity, microvascular thrombosis, and increased nitric oxide (NO) production contribute to microcirculatory dysfunction, inadequate oxygen delivery, and tissue hypoxia (Schouten and others 2008; De Backer and others 2011). In addition, dysfunction of the vascular endothelium and loss of barrier integrity due to inflammation result in capillary leakage and interstitial edema (Goldenberg and others 2011). Likewise, altered alveolar endothelial glycocalyx induces pulmonary edema and lung injury (Maniatis and Orfanos 2008), while disruption of sinusoids is associated with hepatocellular injury and liver dysfunction (Ito and others 2006).

Persistent inflammatory responses also exacerbate the release of ROS and RNS while impairing antioxidant production, leading to oxidative stress damage. These changes alter the energy balance in the mitochondria, leading to cell death (Galley 2011). Moreover, mitochondrial damage causes the release of mitochondrial DNA and formyl peptides, which act as danger-associated molecular patterns recognized by PRRs, worsening organ injury by inducing neutrophil activation (Zhang and others 2010). In addition, some septic patients treated in intensive care units develop disseminated intravascular coagulation (Saito and others 2019).

Cytokines and chemokines activate platelets, neutrophils, and endothelial cells (Iba and Levy 2018). Vascular endothelial cells typically release NO and prostacyclin to maintain an antithrombotic state. However, activated endothelial cells become prothrombotic, producing tissue and von Willebrand factors (Iba and others 2020). Neutrophils, meanwhile, release neutrophil extracellular traps (NETs), composed of DNA, histones, and granule proteins, favoring prothrombotic activity (Camicia and others 2014).

This process causes the formation of microthrombi, which can further potentiate the inflammatory response, aggravating the microvascular dysfunction (Engelmann and Massberg 2013). Furthermore, the consumption of clotting factors generates late hemorrhagic events, which increase mortality (Greco and others 2017).

The immune system has different mechanisms to control inflammation. T regulatory (Treg) cells suppress the activity of $CD4^+$ T cells, B cells, macrophages, neutrophils, and DCs (Okeke and Uzonna 2019). Decoy cytokine receptors such as IL-1 receptor antagonist (IL-1RA), IL-1 receptor type II (IL-1R2), and soluble TNFα receptors (sTNFRs) recognize specific cytokines but are unable to signal (Mantovani and others 2001). Moreover, some anti-inflammatory cytokines, such as TGF-β and IL-10, inhibit the production of proinflammatory cytokines (van der Poll and van Deventer 1999). Also, myeloid-derived-suppressor cells (MDSCs) interfere with T cell responses and regulate cytokine production from macrophages (Gabrilovich and Nagaraj 2009).

Interestingly, after the initial hyperinflammatory phase, some patients with sepsis experience a state of immunoparalysis, which is characterized by downregulation of HLA-DR on myeloid cells and apoptosis of B cells, $CD4^+$ T cells, and follicular DCs (Hotchkiss and others 2001, 2002; Boomer and others 2011). Notably, the CS profile of sepsis also includes anti-inflammatory molecules such as IL-4, IL-10, and TGF-β, and decoy receptors such as IL-1RA and sTNFR (Gogos and others 2000; Surbatovic and others 2015). This immunosuppressive state is responsible for the reactivation of the infection or incidence of secondary infections, which increase sepsis's fatality (Limaye and others 2008; Torgersen and others 2009).

Cytokines also provoke a neuroinflammatory reflex through the afferent vagus nerve. Consequently, efferent vagus projections promote the secretion of acetylcholine by $CD4^+$ T cells, inhibiting the excessive proinflammatory cytokine release (Rosas-Ballina and others 2011). Unfortunately, the immune system cannot return to homeostasis if the primary infection does not resolve and the regulatory mechanisms fail, inflicting more damage without clearing the infection (Fajgenbaum and June 2020). Meanwhile, persistent immunoparalysis can interfere with recovery from critical illness and increase the risk of death. Understanding the interplay of mechanisms that lead to CS and immunoparalysis during sepsis could improve our scientific approaches to other severe infections (Fig. 1).

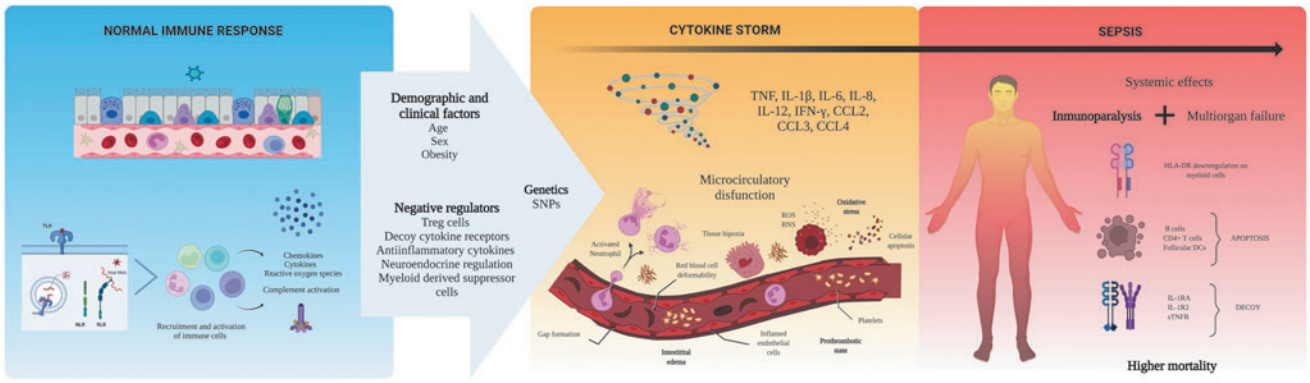

FIG. 1. Mechanisms behind the cytokine storm of sepsis. Sepsis is an exaggerated immune reaction elicited by local or systemic infection. Individuals with this condition display elevated levels of cytokines in the circulation (hypercytokinemia), a phenomenon named ''cytokine storm.'' The mechanisms driving the progression from a normal immune response against a pathogen to sepsis are under investigation. Clinical and demographic features of affected persons, together with genetic factors promoting an excessive immune activation or affecting the regulatory mechanisms of the immune system, might contribute to the pathobiology of sepsis. The exuberant production of cytokines leads to harmful effects on local cells, activation, and increased permeability of the endothelium, and microthrombosis. Hypercytokinemia is also accompanied by many anti-inflammatory mechanisms that arrest immune cell functions (immunoparalysis). Together, these alterations (cytokine storm + immunoparalysis) result in the development of organ failure without clearing the infection. Understanding the pathogenesis of sepsis is crucial to approaching other severe infections such as COVID-19 and pandemic influenza. The art pieces used in this figure were modified from Biorender, licensed under a Creative Commons Attribution 3.0 Unported License. COVID-19, coronavirus disease 2019.

The CSS of Influenza

Immunity against influenza

The influenza virus is among the primary causes of pneumonia, with 290,000–650,000 deaths and 3–5 million cases attributed to this infection annually (Shrestha and others 2011). Influenza generates a broad spectrum of symptoms, from mild to severe disease and death (Ghebrehewet and others 2016; Collaborators 2019). Type A influenza viruses are a source of annual epidemics and major pandemic outbreaks, including the H1N1 in 1918, H2N2 in 1957, H3N2 in 1968, and the most recent H1N1 in 2009 (Dunning and others 2020).

Influenza viruses belong to the Orthomyxoviridae family, and are composed of 4 genres (A to D), from which only A and B infect humans. The structure of the influenza virions has a multisegmented, negative-sense, single-strand (ss) RNA genome of 12–15 kb, with a rounded shape of 80–120 nm in diameter. Inside the capsid, the RNA and the polymerase form a viral ribonucleoprotein (vRNP) complex. The genome is segmented into 8 parts in A and B virus types (7 in C and D), which encode 8 structural proteins (PB1, PB2, PE, hemagglutinin (HA), neuraminidase (NA), M1, M2, NP), and 2 nonstructural proteins (NS1 and NEP).

HA and NA are the major glycoprotein antigens, the first facilitating the entry into the target cell, while NA mediates the release and dissemination of virions from infected cells (Krammer and others 2018). The HA binds to α 2–6 galactose and α 2–3 galactose sialic acid residues in human respiratory epithelial cells and bird gastrointestinal tract cells, respectively (Thompson and Paulson 2021). Once the virus recognizes its cell receptor, it is internalized by clathrin- and caveolin-dependent endocytosis. The vRNPs are imported to the nucleus for replication, mRNA production, and translation of novel proteins to be assembled into a new virion in the cytoplasm (Krammer and others 2018).

The innate airway defenses formed by physical barriers, mucus, phagocytic cells, cytokines, and interferon-stimulated genes (ISGs) are the first protective antiviral barrier (Martin and Frevert 2005). The respiratory epithelium secretes mucins (MUC5AC, MUC5B, MUC1, MUC 4, and MUC16), which prevent the binding of pathogens to epithelial cells (Roy and others 2014; Zanin and others 2016; Hansson 2019). The importance of mucins for defenses against influenza has been demonstrated in studies evaluating the effects of adding synthetic MUC1 molecules to epithelial cell cultures, which managed to restrain influenza viruses. Furthermore, $MUC1^{-/-}$ mice infected with the influenza A virus display higher morbidity and mortality (McAuley and others 2017). Other molecules on the alveolar surface are the surfactant proteins A and D (SP-A and SP-D), which help viral clearance. In influenza, SP-A and SP-D bind to viral HA impeding its activity (Han and Mallampalli 2015).

The immune response against influenza initiates with the recognition of viral PAMPs and downstream signaling via host PRRs (Iwasaki and Medzhitov 2004), from which 3 pathways are essential: endosomal TLR3 and TLR7, cytoplasmatic RIG-1, and the inflammasome (Herold and others 2015). The first 2 lead to the activation of IRF3, IRF7, and NF-κB, promoting the transcription of genes encoding for cytokines, chemokines, and ISGs. RIG-1 is activated by viral ssRNA and signals by interaction with mitochondria-associated antiviral signaling proteins (Yoneyama and others 2015). Failure of RIG-1-mediated sensing of influenza viruses may lead to severe disease (Jørgensen and others 2018). Endosomal TLR3 recognizes dsRNA, and TLR7 recognizes ssRNA, activating the transcription factors NF-κB or IRF7 using signaling pathways downstream of the adapter protein myeloid differentiation factor 88 (MyD88) (Lund and others 2004; Le Goffic and others 2007).

TLR3 also interacts with the adapter Toll/IL-1R domain-containing adapter-inducing IFN-β (TRIF) and activates

serine-threonine kinases (IKKε) and TBK1, which phosphorylates IRF3 for subsequent expression of IFN-β (Le Goffic and others 2007). The third pathway implies the formation of inflammasomes by the NLR family pyrin domain containing 3 receptor (NLRP3), which is expressed in DCs, neutrophils, macrophages, and monocytes. The detection of the viral M2 protein and a polymerase subunit (PB1) provokes the activation of this pathway. The complex is formed by NLRP3, the adapter protein apoptosis-associated speck-like protein (ASC), and procaspase-1. This complex turns on caspase-1, which cleaves the proform of IL-1β (Ichinohe and others 2010).

During influenza, cytokines and chemokines such as type I and III interferons (IFNs), IL-6, CXCL8, CCL2, CCL3, CCL4, and CCL5 are produced at the site of infection (Wareing and others 2004). Type I (IFN-α and IFN-β) and type III IFNs are critical for innate and adaptive antiviral immune responses. They interact with membrane heterodimeric receptors (IFNAR1, IFNRAR2, IFNLR1, Il-10Rβ) associated with Tyk2 and Jak1 kinases, which then phosphorylate STAT-1 and STAT-2, generating 2 activating complexes: IFN-α-activated factor (AAF) and IFN stimulated gene factor 3 (ISGF3). Already in the nucleus, these complexes bind to DNA sequences, IFNγ-activated sequence (SAG), and IFN-stimulated response element (ISRE), resulting in the stimulation of ISGs (Theofilopoulos and others 2005). Interferon-induced transmembrane (IFITM) proteins are among the host ISGs that block viral infection by frustrating cell entry at endosomes (Brass and others 2009).

As such, members of the IFITM family mediate resistance against influenza viruses (Brass and others 2009; Everitt and others 2012; Jia and others 2012; Smith and others 2013; Lanz and others 2015; Yu and others 2015; Blyth and others 2016; Meischel and others 2021; Rohaim and others 2021). Recent clinical investigations in humans have linked increased susceptibility to influenza with specific single-nucleotide polymorphisms (SNPs) in genes coding IFITM1 and IFITM3 (Everitt and others 2012; Zhang and others 2013; Allen and others 2017; Kim and others 2020, 2021).

Other cytokines and chemokines recruit neutrophils, monocytes, macrophages, NK cells, and DCs. NK cells recognize viral HA molecules through their NKp44 and NKp46 receptors and induce direct cytotoxicity or recognize infected cells through their low-affinity Fc gamma receptor FcRIIIa (CD16) that binds to IgG antibodies, leading to antibody-mediated cellular cytotoxicity (ADCC). NK cells can also release granular granzyme and perforin to induce cell lysis and secrete cytokines such as TNFα and IFNy (Jegaskanda and others 2019). Alveolar macrophages (AMs) engulf infected cells and release proinflammatory cytokines and chemokines (CCL2, CCL3, CCL4, CCL5, and TNFα) to recruit circulating monocytes, which in turn change their phenotype toward inflammatory macrophages. The latter releases CCL5, CXCL9, and CXCL10 to increase the recruitment of other leukocytes, mainly neutrophils (Latino and Gonzalez 2021).

Neutrophils migrate to the infection site and mediate phagocytosis, degranulation, the release of NETs, secretion of chemokines and cytokines (CXCL8, TNFα), and ROS production. Excessive neutrophil recruitment and degranulation destroy the lung extracellular matrix and induce epithelial apoptosis and alveolar lesions (Camp and Jonsson 2017). DCs engulf pathogens, present antigens to B and T cells, provide costimulatory signals (CD40, CD80, and CD86), and secrete cytokines (Shekhar and others 2018). The cDC2 subtype is a source of proinflammatory cytokines in the lung, whereas plasmocytoid DCs liberate large amounts of type I IFNs in response to viral infection (Thomas and others 2014).

Adaptive immunity is essential for viral clearance. $CD4^+$ T cells recognize viral antigens presented by APCs on MHC-II molecules. Th1 cells produce IFNγ, IL-2, and TNFα, activating macrophages and promoting B cells to produce antibodies. Th2 lymphocytes produce IL-4, IL-5, and IL-13 and support isotype class switching in B cells (Brown and others 2006). Notably, a $CD4^+$ T cell response imbalance toward the predominance of Th2 functions is detrimental to immunity against some respiratory viruses (Moran and others 1999; Pinto and others 2006). During influenza, $CD8^+$ T cells are activated in the lymph nodes and migrate to the infection site, where they kill infected cells by apoptosis via Fas/FasL and perforin and granzyme degranulation (Brincks and others 2008). B lymphocytes produce neutralizing antibodies against HA and NA, which activate the complement and elicit NK cell ADCC (Stadlbauer and others 2019; Turner and others 2020b).

Cytokine signatures of severe influenza

All the signaling pathways and cells initially deployed against influenza benefit the host by preventing viral replication and shedding; however, these mechanisms cause organ dysfunction among patients who progress to severe disease. As for sepsis, the factors that determine the switch from a protective to a harmful immune reaction are yet unclear. Perhaps host and pathogen features contribute in different proportions to establishing a CSS.

Different demographic and clinical host factors, such as sex, age, and obesity, may be involved in the susceptibility to severe influenza. Accordingly, extreme age represents a risk factor for the severity of influenza (Casalino and others 2017). In this regard, the immune system of the young can generate a strong response, whereas in the elderly, the immune response is not regulated appropriately (Aiello and others 2019). Sex was a significant prognostic factor during the 2009 pandemic since most patients hospitalized for severe disease were young women (Klein and others 2012). Finally, obese individuals with influenza display higher morbidity and mortality. High leptins and free fatty acids in obese patients might activate TLRs, monocytes, and lymphocytes to produce inflammatory cytokines (Honce and Schultz-Cherry 2019).

Genetic factors might also play a role in severe respiratory infections. Accordingly, SNPs conditioning the dysfunction of PRRs, signaling molecules, transcription factors, cytokines, chemokines, or their receptors might make an individual prone to excessive immune activation after influenza virus infection (Forbester and Humphreys 2021). Importantly, these genetic variations may lead to CS when other determinants such as the pathogen virulence, viral load at the lung, and the demographic features described above act together (de Jong and others 2006).

The immune profile observed in the circulation, bronchoalveolar lavage (BAL), and lung specimens of severely ill influenza patients is characterized by large concentrations of

TNFα, IFNy, IL-1β, IL-2, IL-6, CXCL8, CCL2, CCL3, CXCL10, G-CSF, FGF, VEGF, and anti-inflammatory mediators such as TGF-β, IL-10, and IL-1RA (Meduri and others 1995; Estella 2011; Lee and others 2011; Paquette and others 2012; Bautista and others 2013; Gao and others 2013; Rendón-Ramirez and others 2015; Fiore-Gartland and others 2017; Mudd and others 2020; Choreño-Parra and others 2021a; Reynolds and others 2021; Xie and others 2021). These cytokines generate lung damage when overproduced by different mechanisms, some of which were mentioned above. Their damaging properties cannot be experimentally tested in humans, but animal models have proven that these cytokines mediate the morbidity and mortality of influenza.

An important cytokine for antiviral defenses that plays a pathogenic role during severe influenza is IFNy, mainly produced by adaptive Th1 cells. In mice with influenza A (H1N1), antibody neutralization of IFNy reduces lung tissue inflammation and BAL cytokine levels, and improves survival (Liu and others 2021). IL-1β is another cytokine harmful during influenza. Indeed, mice with genetic deficiency of the inflammasome complex NLRP3/ASC/caspase-1 are less susceptible to lung inflammation and mortality by viral H7N9 influenza infection (Ren and others 2017). Finally, IL-6 favors neutrophil recruitment and B cell differentiation. However, its excessive secretion is linked to severe illness. Importantly, inhibition of IL-6 by the suppressor of cytokine signaling 3 (SOCS-3) improves influenza outcomes by reducing inflammation in mice (Liu and others 2019).

The data summarized above indicate that cytokines produced by strong immune responses cause severe manifestations of influenza. Although the mechanisms of predisposition to the CSS are not well defined, lessons from the study of sepsis and influenza pathogenesis might be important to approach other infections such as COVID-19.

The CSS of COVID-19

Immunity against SARS-CoV-2

SARS-CoV-2 is an enveloped, positive-sense ssRNA virus of the Coronaviridae family, genus Beta coronavirus, including SARS-CoV and MERS-CoV (Wu and others 2020b; Zhou and others 2020a). Its genome contains 14 major open reading frames (ORFs) coding for nonstructural, accessory, and structural proteins. The ORFs 10 and 11 encode for 4 structural proteins named spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Lim and others 2016). The S protein attaches to the cellular receptor angiotensin-converting enzyme metallopeptidase 2 (ACE2), thus determining infectivity and viral tropism (Li 2016). This enzyme is found in the lungs, blood vessels, small intestine, and kidney, among other organs, suggesting alternative transmission routes and explaining the multiorgan damage observed in critically ill COVID-19 patients (Hamming and others 2004). CD147 has been proposed as another SARS CoV-2 receptor (Wang and others 2020a).

Meanwhile, protein E is a viroporin that participates in releasing newly assembled viral particles. Studies in SARS-CoV have shown that the deletion of protein E does not affect viral production but reduces virion maturation and viral load (Schoeman and Fielding 2019). In addition, the E protein has a lower mutational rate than the S protein, making it a candidate target for vaccines (Sarkar and Saha 2020). Protein M is capable of binding to all the other structural proteins. Despite its undefined function, its binding to the N protein allows its stabilization and, therefore, indirectly participates in the viral genome assembly. Also, the structure of M protein suggests a potential sugar transporter function such as the sugar transporter SemiSWEET protein found in prokaryotic cells (Thomas 2020).

Finally, protein N is among the most abundant and immunogenic SARS-CoV-2 proteins that participate in the transcription and assembly of the viral genome and immune evasion (Cubuk and others 2021).

The most common SARS CoV-2 infection route is the respiratory system. In this study, the S protein binds to ACE2 in the plasma membrane of pneumocytes. This protein owns 2 functional domains: the S1 domain contains the receptor-binding domain, which attaches to ACE2, whereas the S2 domain mediates the fusion of the viral and host cell membranes (Walls and others 2020). For effective infection, the host transmembrane serine protease-2 (TMPRSS-2) cleaves to the S2 subunit of the protein (Glowacka and others 2011; Matsuyama and others 2020). Other host proteases such as furin, TMPRSS4, and cathepsin L also activate the S2 protein (Ou and others 2020; Zang and others 2020). Recently, neuropilin-1 has been identified as another host factor facilitating SARS-CoV-2 infectivity (Hoffmann and others 2020; Matsuyama and others 2020).

The entry mechanisms of coronaviruses are unclear. Initially, researchers thought that SARS-CoV entry was by the direct release of viral particles into the cells after complete membrane fusion. However, SARS-CoV and SARS-CoV-2 also utilize clathrin-dependent endocytosis (Wang and others 2008; Bayati and others 2021).

As for influenza viruses, mucins and collectins at mucosal respiratory barriers play an essential role against SARS-CoV-2 (Bose and others 2021). Accordingly, increased MUC1 and MUCl5AC have been observed in the sputum of patients with COVID-19 (Lu and others 2021). Also, animal studies demonstrated that MUC4 protects the female, but not male mice from SARS-CoV-2 (Plante and others 2020). Surfactant proteins with immune properties may also participate in airway antiviral defenses. Indeed, elevated levels of SP-D have been observed in the blood of patients with severe COVID-19 (Tong and others 2021), suggesting a leakage from the airway due to alveolar damage.

This blood translocation of SP-D might be less severe than in influenza (Choreño-Parra and others 2021b), but could be used as a lung injury readout. Interestingly, recombinant fragments of SP-D bind and neutralize the viral S protein functions (Hsieh and others 2021), while mannose-binding lectin recognizes glycosylated sites of the S protein neutralizing SARS-CoV-2 infectivity (Stravalaci and others 2022).

The PRRs that recognize SARS-CoV-2 and initiate the immune responses remain obscure. As this virus is genetically related to SARS-CoV, both viruses may share mechanisms of infection. For instance, SARS-CoV is recognized by TLR3 and TLR4, which induce MyD88 and TRIF pathways (Sheahan and others 2008; Totura and others 2015). TLR4 has been proposed to detect SARS-CoV-2 (Aboudounya and Heads 2021), but complementary evidence is required. TLR2 also recognizes the E protein of

SARS-CoV-2 and activates MyD88 signaling to initiate the production of IL-1β, IL-6, TNFα, IFNy, and CXCL10 (Zheng and others 2021). Finally, the viral RNA sensors TLR3 and TLR7 promote the release of type I and type III IFNs, IL-1β, IL-4, IL-6, and IFNy, through IFR3 and NFκB pathways (Bortolotti and others 2021). In addition, SARS-CoV triggers the bioactivation of IL-1β through NLRP3 inflammasomes (Shi and others 2019).

Similarly, SARS-CoV-2 N protein promotes NLRP3 inflammasome activation (Pan and others 2021), explaining the high levels of IL-1β observed in COVID-19 patients (Rodrigues and others 2021).

Type I interferons and ISGs are strongly upregulated during SARS-CoV-2 infection (Lee and others 2020; Mantlo and others 2020; Rosa and others 2021). Indeed, higher levels of IFN-α, IFN-β, IL-2, and IL-12 are distinctive features of asymptomatic and mild as opposed to severe COVID-19 (Masood and others 2021; Tjan and others 2021). Type I IFNs reduce the infectivity of SARS-CoV-2 *in vitro* (Mantlo and others 2020), whereas IL-2 and IL-12 might contribute to protection by stimulating T and B cell growth and differentiation. Among other ISGs transcribed during COVID-19, IFITMs might be necessary, and some studies have linked the prevalence of SNPs affecting *IFITM3* to COVID-19 susceptibility (Gómez and others 2021; Schönfelder and others 2021).

The initial recognition of SARS-CoV-2 also promotes chemotaxis. Noticeably, in patients with severe COVID-19, an ample range of immune cell subtypes are depleted from the circulation, including monocytes, DCs, $CD4^+$ T cells, $CD8^+$ T cells, B cells, and NK cells. This phenomenon is accompanied by peripheral neutrophilia and intense leukocyte infiltration of the lung (Liao and others 2020; Merad 2020; Wang and others 2020b; Wang and others 2020; Xu and others 2020; Zheng and others 2020), suggesting the potential participation of specific immune cell subsets in defenses against SARS-CoV-2.

Neutrophils are the principal cells recruited to the lung of COVID-19 patients. These cells degranulate, phagocyte the virus, and liberate NETs (Wu and others 2020a; Reusch and others 2021; Rosa and others 2021). However, their exuberant recruitment and function lead to tissue damage and a readout of COVID-19 severity (Hernández-Cárdenas and others 2021). In the lung, distinct AM subpopulations engulf SARS-CoV-2 to initiate the local immune response. However, the virus can escape from these cells and evade innate immunity (Dalskov and others 2020; Lv and others 2021). Then, attracted by chemokines such as CCL2, CCL3, and CCL4, monocytes and macrophages migrate to contribute to antiviral defenses by phagocytosis of virus and infected cells and cytokine production to amplify the response. Nevertheless, intense recruitment of inflammatory monocytes causes excessive production of proinflammatory molecules and neutrophil infiltration, which might lead to injury (Merad 2020; Vanderbeke and others 2021).

Populations of adaptive NK cells with enhanced cytotoxic functions may also participate in antiviral defenses, as indicated by studies demonstrating increased circulation of $NKG2C^+$ memory-like NK cells in patients with COVID-19 (Maucourant and others 2020). Interestingly, deleting mutations in genes coding for NKG2C and its ligand HLA-E and dysfunction of NK cells are associated with a higher risk of severe COVID-19 (Krämer and others 2021; Vietzen and others 2021). Moreover, NK cells from severe COVID-19 patients express PD-1, a marker of functional exhaustion (Wilk and others 2020).

The initiation of adaptive immune responses is pivotal for infection control, viral clearance, and short-term protection against reinfection, as demonstrated in studies of COVID-19 vaccines (Folegatti and others 2020; Ewer and others 2021; Levin and others 2021; Lustig and others 2021). In this regard, vaccination and natural infection with SARS-CoV-2 elicit germinal center (GC) reactions at secondary lymphoid organs where B cells activate and differentiate into plasma cells that produce neutralizing antibodies with the cooperation of follicular T helper cells (Shaan Lakshmanappa and others 2021; Turner and others 2021a, 2021b). Significantly, the failure in follicular T cell activation and promotion of GCs is associated with severe COVID-19 (Kaneko and others 2020).

Finally, cytotoxic $CD8^+$ T cells also participate in SARS-CoV-2 elimination and may be particularly important against novel coronavirus variants with improved evasiveness of humoral immunity (Naranbhai and others 2022). Figure 2 summarizes the current knowledge about defensive immune mechanisms against SARS-CoV-2 and how they compare with immunity versus influenza.

Cytokine signatures during severe COVID-19

A better understanding of the immune factors implicated in the pathophysiology of COVID-19 is crucial to guiding the development of novel vaccines and immunotherapeutics. Unfortunately, what we comprehend about severe COVID-19 is contradictory. First, the immune response against SARS-CoV-2 is overregulated. Nevertheless, this excessive reaction is not protective and instead causes tissue injury. Patients with severe COVID-19 display elevated levels of proinflammatory and anti-inflammatory cytokines, chemokines, and growth factors, accompanied by increased neutrophil counts, lymphopenia, and depletion of different cellular subsets in the circulation, as mentioned above.

The factors aiding the transition from a protective to a dysregulated immune response are elusive, but there is much interest in identifying risk factors associated with worse clinical outcomes in COVID-19. Again, clinical variables such as age and sex are important. Aging is associated with declined immunity and confers higher odds of death in patients with COVID-19 (Costagliola and others 2021). For instance, elderly humans and primates display increased neutrophilic inflammation than young individuals after SARS-CoV-2 infection (Rosa and others 2021). Remarkably, the male gender is disproportionally associated with worse outcomes in COVID-19. The higher expression and distinct tissue distribution of ACE2 and the possible immune alterations common in males might explain this discrepancy (Peckham and others 2020). The ample spectrum of immune deficiencies induced by metabolic disruption might account for the higher risk for severe COVID-19 in obese and in diabetic patients (Holly and others 2020).

In contrast, host genetic factors determining higher susceptibility to CS are poorly recognized since recent studies have only identified genetic abnormalities conditioning immune dysfunction, but not hyperinflammation (Forbester and Humphreys 2021; Velavan and others 2021).

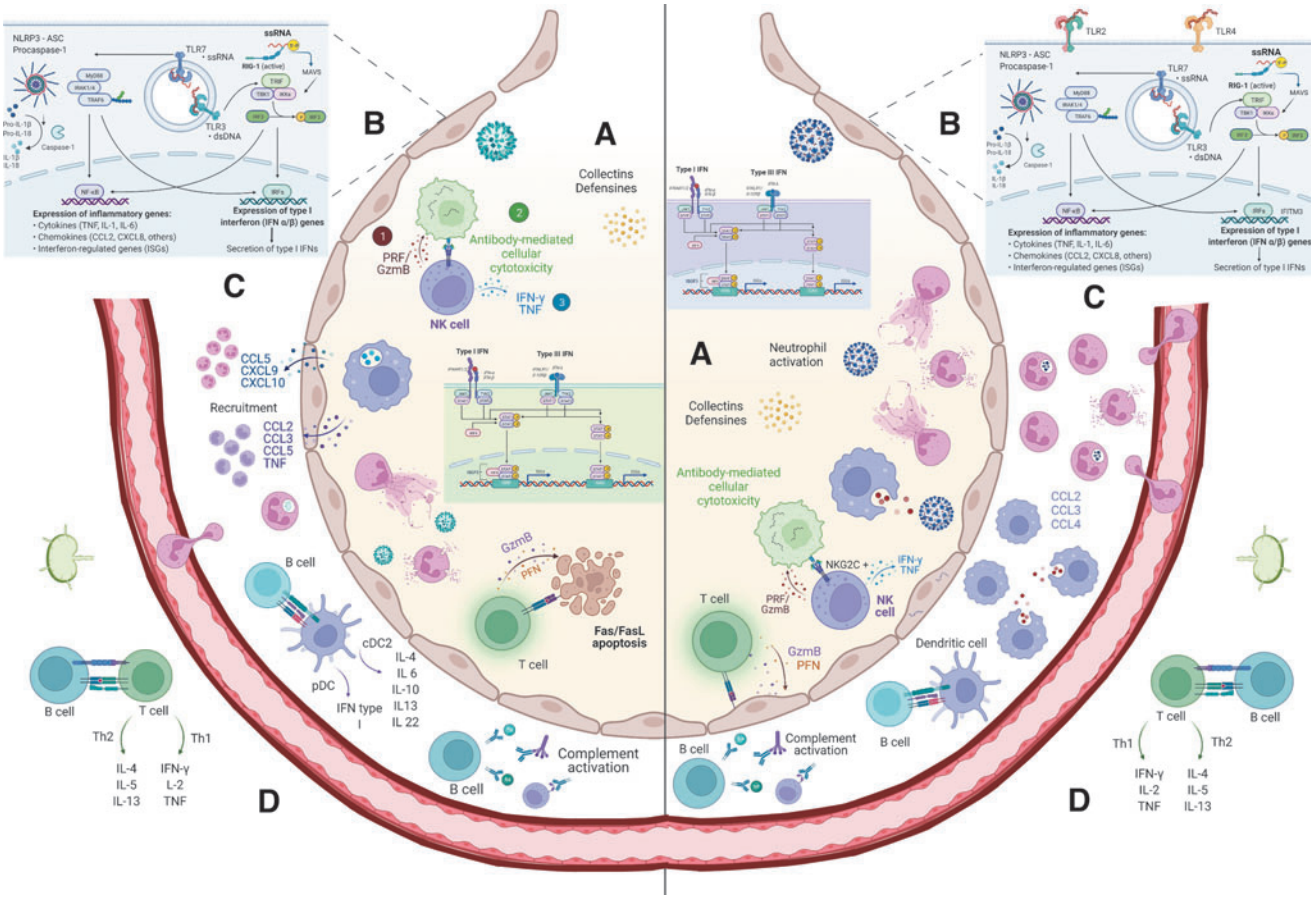

FIG. 2. Immune mechanisms implicated in the defense against SARS-CoV-2 and influenza. **(A)** Innate humoral factors present in the lumen of the lower airways block viruses before they attach the underlying epithelium. Mucins and surfactant proteins A and D are important for host defenses against influenza virus and SARS-CoV-2. Mannose-binding lectin has also shown to neutralize SARS-CoV-2. **(B)** The innate immune response against these viruses begins with recognizing PAMPs by host PRRs. TLR3, TLR7, RIG-1, and the NLRP3 inflammasome participate in the early recognition of influenza and SARS-CoV-2, eliciting the production of cytokines, chemokines, and interferons. TLR2 and TLR4 may also participate in the defense against SARS-CoV-2, but the evidence is still scarce. **(C)** The innate phase of the immune response against influenza and SARS-CoV-2 comprehends an ample range of mechanisms, including the chemotaxis of monocytes, neutrophils, other granulocytes, and neutrophil degranulation and NETosis, phagocytosis of viral particles and infected cells, and cytotoxicity by NK cells. Some populations of NK cells with adaptive properties ($NKG2C^+$) might also expand during COVID-19. **(D)** Dendritic cells link innate and adaptive immunity by presenting antigens at local lymph nodes and secreting cytokines that shape the functional fate of B and T cells. B cells produce neutralizing antibodies that mediate complement activation and antibody-dependent cellular cytotoxicity. $CD8^+$ T cells kill infected cells by perforin and granzyme degranulation or via the Fas/FasL signaling pathway. $CD4^+$ T cells produce cytokines to orchestrate all the other mechanisms described. A balance between Th1 and Th2 responses might be crucial for antiviral immunity. The art pieces used in this figure were modified from Biorender, licensed under a Creative Commons Attribution 3.0 Unported License. NK, natural killer; NLRP3, NLR family pyrin domain containing 3 receptor; RIG-1, retinoic-acid-inducible gene 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR, Toll-like receptor.

Profiling immune mediators in severe COVID-19 patients have revealed low concentrations of type I interferons (Hadjadj and others 2020; Masood and others 2021), and elevated levels of TNFα, IFNy, IL-1β, IL-1RA, IL-4, IL-6, IL-7, CXCL8, IL-9, IL-17A, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CXCL9, CXCL10, G-CSF, GM-CSF, PDGF, FGF, and VEGF (Chen and others 2020; Han and others 2020; Huang and others 2020; Kong and others 2020; Lucas and others 2020; Remy and others 2020; Wan and others 2020; Yang and others 2020; Zhu and others 2020b; Reynolds and others 2021; Sims and others 2021). From these, CXCL10, a downstream IFNy effector molecule, shows a strong correlation with disease severity (Yang and others 2020) and is highly detectable in the airways of COVID-19 patients (Reynolds and others 2021).

This chemokine, together with CXCL8, recruits neutrophils after binding to CXCR3 (Ichikawa and others 2013), thus exacerbating neutrophil-induced lung damage (Wilk and others 2020; Rosa and others 2021; Vanderbeke and others 2021). CXCR3 is also expressed on macrophages, activated Th1 cells, B lymphocytes, NK cells, and DCs (Groom and Luster 2011). Hence, CXCL10 might be a suitable target to reduce lung inflammation in COVID-19 patients. Meanwhile, the role of IL-9, the classical cytokine of Th9 cells, is unknown in COVID-19.

However, the magnitude of Th9 responses has been associated with the severity of respiratory syncytial virus infection (Pinto and others 2006). CCL5 is chemotactic for T cells, eosinophils, and basophils expressing the receptor CCR5, and its blockade reduces inflammation and viremia in critically ill COVID-19 patients (Patterson and others 2020), whereas CCL7 attracts monocytes and eosinophils and is associated with the severity of the disease (Yang and others 2020). GM-CSF is a myeloid cell growth factor and proinflammatory signal instructing macrophages to amplify cytokine cascades. GM-CSF is secreted by macrophages, T cells, mast cells, NK cells, endothelial cells, and fibroblasts and might be a pivotal driver of lung inflammation in severe COVID-19 (Leavis and others 2022). Notably, the GM-CSF blockade improves clinical symptoms and survival in patients with COVID-19 (De Luca and others 2020).

Intriguingly, the CS of severe COVID-19 is also accompanied by functional impairment of myeloid cells and lymphocytes (Remy and others 2020), resembling the immunoparalysis that accompanies hypercytokinemia in sepsis. Impaired type I IFN production might advocate this immunocompromised state (Hadjadj and others 2020; Masood and others 2021). Also, mixed signals might provide immune cells with confounding instructions making them functionally impaired. Indeed, different patterns of cytokine and chemokine combinations in COVID-19 patients can be identified according to their disease trajectory, showing that some individuals with the worse outcomes display mixed polyfunctional cytokine signatures (Lucas and others 2020). Furthermore, the anti-inflammatory cytokines TGF-β and IL-10 have been detected in high concentrations during SARS-CoV-2 infection and might suppress immune cell functions (Han and others 2020; Wan and others 2020; Ferreira-Gomes and others 2021).

Face-to-Face: Immune Profiles of Severe Influenza and COVID-19

As remarked in the article, the study of sepsis and severe influenza has provided reference knowledge to face COVID-19. Currently, it is accepted that the clinical landscape of COVID-19 mirrors other infectious CSS in many aspects. This assumption relies on literature reviews and retrospective studies highlighting similarities between patients infected with SARS-CoV-2 and influenza (Jiang and others 2020; Tang and others 2020). Indeed, several symptoms are shared by both infections, probably due to a similar pathophysiology. Nonetheless, detailed analysis reveals that some clinical features distinguish each disease, perhaps because of molecular properties, tropism determinants, and virulence factors of each virus. Table 1 summarizes the main similarities and differences in viral characteristics and clinical findings of COVID-19 and influenza. The rest of this section focuses on comparing the CSS of both diseases.

The potential behind similarities

Using the data summarized here, we can conclude that the CSS of severe COVID-19 coincides with influenza, indicating common pathological mechanisms that could be exploited for therapeutic purposes. Certainly, both viruses are recognized by similar PRRs, trigger the same signaling

Table 1. Viral and Clinical Characteristics of COVID-19 and Influenza

Characteristic	*Influenza*	*COVID-19*
Virus identification	1918, United States	2019, China
Virus family	Orthomyxoviridae	Coronaviridae
Viral nucleic acid	Single-stranded RNA (negative sense) 13.5 kb	Single-stranded RNA (positive sense) 26–32 kb
Animal reservoirs	Birds, pigs	Bats? Pangolin?
Mechanism of transmission	Inhalation	Inhalation
Incubation period	2 days	2–14 days
R0	2	2.5
Genome variation mechanism	Reassort and rearrange	Point mutations
Viral proteins of interest	HA, NA	*S*, E, M
Host receptor	α 2,6 sialic acids	ACE2
Tropism	Respiratory tract epithelium	Multiple organs
Frequent symptoms	Fever, dyspnea, cough	Fever, dyspnea, cough
Distinctive manifestations	High fever, headache, fatigue, myalgia, sore throat, cough, eye symptoms	Nonproductive cough, fatigue, myalgia, gastrointestinal symptoms, anosmia, dysgeusia
Radiological findings	Multilobe consolidations	Ground-glass opacities
High-risk populations	Elderly, pregnant women, people with respiratory diseases, hypertension, coronary heart disease, diabetes, kidney disease, liver disease, malignancy	Elderly, people with respiratory diseases, obesity, hypertension, coronary heart disease, diabetes, malignancy
Need for hospitalization	5.6%	20%
Need for intubation	4.8%	10%–15%
Mortality	0.13%–1.36%	1.40%–3.67%
Sequela	20%–30%	25%–40%

ACE2, angiotensin-converting enzyme metallopeptidase 2; COVID-19, coronavirus disease 2019; HA, hemagglutinin; NA, neuraminidase.

pathways, and require similar innate and adaptive immune components for protection. As shown in panel A of Fig. 3, the CS of severe influenza and COVID-19 concurs in elevated PRR- and inflammasome-induced cytokines, such as TNFα, IL-1β, and IL-6, revealing a persistent innate inflammatory reaction that is detrimental to the host. Hypothetically, targeting these molecules could reduce their vascular and immunological effects, which are key in the pathogenesis of sepsis, calming inflammation and allowing the lung and extrapulmonary organs to restore homeostasis.

To this matter, broad transcriptional suppression of innate inflammatory genes might be achieved using corticosteroids. For instance, dexamethasone effectively reduces the morbidity of patients with severe COVID-19 (Group and others 2021). This drug has minor mineralocorticoid effects and reduces inflammation by enhancing the deacetylation of the histones that regulate cytokine gene expression (Barnes 2006). Conversely, corticosteroids increase the rates of co-infection and death in patients with influenza (Zhou and others 2020b), although recent trials indicate a potential benefit for survival (Villar and others 2020).

Direct blockade of TNFα (infliximab), IL-1R (anakinra, canakinumab), IL-6 (siltuximab, olokizumab), and IL-6R (tocilizumab, sarilumab, levilimab) is being tested in clinical trials, showing promising benefits by reducing symptomatic burden, need for invasive respiratory support, and death, thus warranting further investigation, as revised elsewhere (Pum and others 2021). TNFα antagonism would warrant additional research about the timing of treatment administration since TNFα is potentially protective during the early stages of influenza and SARS-CoV-2 infection. Some observations of individuals already taking anti-TNFα therapies that showed milder symptoms after getting positive for COVID-19 might dissipate this concern (Abdullah

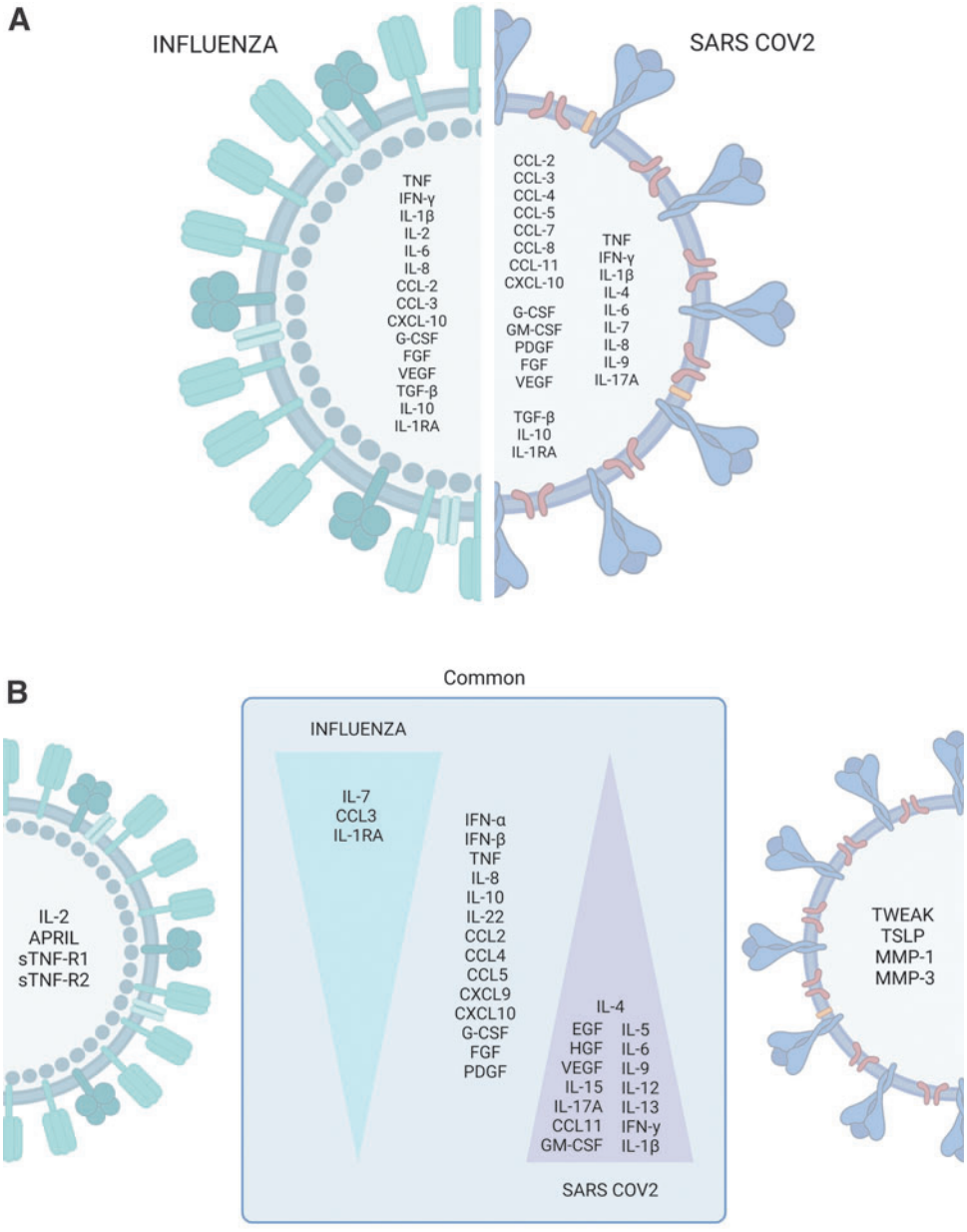

FIG. 3. The cytokine storm profiles of pandemic influenza and COVID-19. **(A)** Cytokines, chemokines, and growth factors commonly or differentially elevated during severe influenza and COVID-19 were identified by retrospective analysis of independent studies. **(B)** Immune profiles distinguishing influenza from COVID-19 identified by parallel comparisons. The art pieces used in this figure were modified from Biorender, licensed under a Creative Commons Attribution 3.0 Unported License.

and others 2020). On the contrary, tocilizumab is among the immunotherapies most extensively evaluated in COVID-19. By the time SARS-CoV-2 emerged, this agent had already proven safety and efficacy against other CSS (Yokota and others 2008; Kotch and others 2019), facilitating its rapid reallocation.

Although most studies show clinical benefits, data supporting tocilizumab lack reproducibility (Price and others 2020), perhaps because of methodological heterogeneity of clinical trials. Meanwhile, there is little evidence regarding the use of tocilizumab in patients with influenza. Two small studies have shown that patients previously receiving this treatment display milder symptoms of infection (Kawada and others 2013), and tocilizumab does not affect antibody responses against influenza vaccines (Mori and others 2012), supporting that tocilizumab could be safely used for influenza patients. A relevant aspect to consider for anti-IL-6 immunotherapy of infectious CSS is the effects of IL-6 on adaptive immunity and T cell differentiation, which vary depending on the concentration of other cytokines in the milieu (Martinez-Sanchez and others 2018), and, if altered, could lead to detrimental effects.

Hence, tocilizumab administration should be guided not only by IL-6 concentrations but also by each patient's cytokine and immune cell profile. This premise might apply to other immunotherapeutics as well.

Remarkably, severe influenza and COVID-19 also converge in elevated levels of chemotactic (CXCL8, CCL2, CCL3, and CXCL10) and activating molecules (G-CSF) acting on monocytes and neutrophils. As mentioned above, a range of monocyte and neutrophil subsets with inflammatory and degranulating phenotypes mediate lung inflammation and disease progression in influenza and COVID-19 (Turner and others 2020a; Wilk and others 2020; Rosa and others 2021; Vanderbeke and others 2021). Hence, disruption of these chemotactic axes is also an attractive therapeutic approach. Currently, only a clinical trial is evaluating the effect of an anti-CXCL8 antibody for the treatment of COVID-19 (NCT04347226), but no results have been posted. Therefore, more research on the antagonism of CXCL8, CCL2, CCL3, and CXCL10 in influenza and COVID-19 is required.

Interestingly, innovative approaches to disrupt chemotaxis using molecular engineered decoy CCL2 and CXCL8 proteins deserve additional evaluation (Adage and others 2015a, 2015b; Roblek and others 2016). Despite this, inhibiting chemotaxis could require administering various agents at a time because of the considerable redundancy of the human chemokine axes. The side effects of CXCL10 blockade in immune protection against influenza and COVID19 should also be tested due to the functions of this chemokine in mobilizing T cells. Similarly, the therapeutic potential behind antagonizing G-CSF has not been addressed, but recent observations of detrimental consequences of the opposite approach (G-CSF administration) in COVID-19 patients are proof of the concept (Taha and others 2020; Sereno and others 2021).

Historically, IFNy has been considered the dominant protective mechanism against intracellular pathogens. In contrast, in the light of fresh visions, IFNy-mediated Th1 responses are highly destructive backup responses only deployed when innate defenses fail in clearing infections (Matzinger and Kamala 2011). High levels of IFNy in patients with severe but not mild-to-moderate influenza and COVID-19 reinforce this idea. Emapalumab, a monoclonal antibody against IFNy, is safe and effective in reducing the CSS of primary HLH (Locatelli and others 2020), and is currently under evaluation for CSS of severe COVID-19 (NCT04324021).

Immune mediators with strong effects on the endothelium, such as FGF and VEGF, are also potential objectives of immunotherapy to reduce morbidity derived from microvascular abnormalities during severe influenza and COVID-19. VEGF is of particular interest as this marker correlates with acute kidney injury development and progression to severe disease in influenza and COVID-19 patients, respectively (Bautista and others 2013; Kong and others 2020). VEGF inhibition with bevacizumab is used harmlessly to reduce angiogenesis associated with lung cancer and ocular disorders (Lauro and others 2014; Afarid and others 2018).

A small phase 2 study has shown some clinical potential of bevacizumab in critically ill patients with COVID-19 (Pang and others 2021), but the evidence is still scarce. Lastly, the interruption of the effects of elevated TGF-β, IL-10, and IL-1RA levels might help overcome the immune cell exhaustion and immunosuppression that accompany the CS of these infections. However, extensive experimentation is required before clinical applications are attempted since molecules such as TGF-β and IL-10 have concentration-dependent effector and regulatory properties, such as promoting IgA production in epithelia.

Influenza versus COVID-19: targeting differences

Beyond the parallelisms between influenza and COVID-19 aforesaid, a compilation of retrospective data from independent studies indicate that IL-2 increases only during severe influenza, whereas high concentrations of IL-4, IL-7, IL-9, IL-17A, CCL4, CCL5, CCL7, CCL8, CCL11, GM-CSF, and PDGF are exclusive features of severe COVID-19 (Fig. 3A). So, what is clear is the ample and polyfunctional CS profile elicited by SARS-CoV-2 but not the influenza virus. Nevertheless, to identify distinctive CS components of COVID-19 and influenza, the problem with retrospective comparisons is the risk of biased conclusions due to differences in the genetic background, sociocultural characteristics, technological infrastructure, and research logistics in different regions.

Another caveat is that molecules identified by this approach are observed in severe but not mild-to-moderate forms of each disease, without side-to-side contrasting of both infections. Furthermore, some cytokines could be measured independently in one disease group but not the other. Hence, parallel analyses in geographical settings with similar resources would provide a better perspective. Surprisingly, although the emergence of SARS-CoV-2 occurred near the peak of the 2019–2020 influenza season (Poyiadji and others 2020; Zhu and others 2020a), only a few comparative studies have been conducted (Lee and others 2020; Mudd and others 2020; Vaz de Paula and others 2020; Choreño-Parra and others 2021a, 2021b, 2021c; Guo and others 2021; Olbei and others 2021; Reynolds and others 2021), which has also been difficulted by a reduction in the circulation of influenza viruses following the COVID-19 pandemic.

As shown in Fig. 3B, data from parallel comparisons exhibit a broad spectrum of elevated molecules in both diseases. From these, several cytokines with antiviral (IFN-α, IFN-β), inflammatory (TNFα, IL-12, IL-22), regulatory (IL-10), chemoattractant (CXCL8, CCL2, CCL4, CCL5, CXCL9, CXCL10), angiogenic (FGF, PDGF, PDGF), and growth factor (G-CSF, FGF, PDGF) properties are constantly upregulated in severe influenza and COVID-19. These findings provide further rationale for immunotherapy directed to regulate innate inflammation, monocyte/neutrophil chemotaxis, and vasoactive cytokines to reduce the morbidity associated with these CSSs.

The second category of molecules is only elevated in one disease but not the other. For instance, severe influenza differs from COVID-19 by higher levels of IL-2, APRIL, sTNF-R1, sTNF-R2, SP-D, and CXCL17. These mediators exert important functions to sustain protective immunity. IL-2 and APRIL support T cell and plasma cell survival (Benson and others 2008), respectively, while sTNF-R1/R2 are decoy receptors that balance the destructive capacity of TNFα (Pennica and others 1993). CXCL17 is a mucosal chemokine expressed in the respiratory tract that mediates myeloid-cell recruitment and anti-inflammatory activities (Choreno-Parra and others 2020). The elevated CXCL17 levels observed only in severe influenza patients might indicate that they have more regulatory mechanisms to minimize tissue damage than individuals with COVID-19. Thus, immunotherapy against these factors might not be suitable, but the observations reveal important differences in the pathogenesis of influenza.

Conversely, TWEAK, TSLP, MMP-1, and MMP-3 are upregulated only in COVID-19. TWEAK is an amplifier of inflammation that stimulates the further secretion of IL-6, CXCL8, CXCL10, and MMP-1 (Saas and others 2000; Chicheportiche and others 2002). Therapeutic targeting of TWEAK might calm inflammation and reduce the morbidity of COVID-19. Since TWEAK might promote cancer cell survival, a monoclonal antibody developed to block the TWEAK receptor (enabatuzumab) is being tested clinically in cancer trials (Lam and others 2018), although it has possible hepatotoxic effects. TSLP is a promoter of allergic inflammation and Th2 responses (Ito and others 2012). The matrix metalloproteinases MMP-1 and MMP-3 are implicated in tissue damage underlying other lung diseases (D'Armiento and others 1992; Dahlen and others 1999; Greenlee and others 2007), placing them as potential therapeutic objectives to reduce lung injury in COVID-19. Nonetheless, validation studies are required to demonstrate a link between TWEAK, TLSP, MMP-1, and MMP-3 and severe COVID-19.

A third cytokine cluster includes molecules found in severe influenza and COVID-19, but with higher frequency and concentrations in one CSS than its counterpart. Interestingly, the profile of this cluster in COVID-19 again shows a mixed Th1/Th2/Th9/Th17 response, together with innate cytokines (IL-1β, IL-6), eosinophil chemokines (CCL11), growth factors, and vasoactive molecules (GM-CSF, HGF, EGF, VEGF). Hence, the lack of balance of the effector response might be another determinant of the host defensive collapse observed in some critical COVID-19 patients. Specifically, the Th2 component of this response might inhibit antiviral responses in specific subgroups of patients and generate interstitial infiltrates of neutrophils, eosinophils, and type 2 innate lymphoid cells (ILC2s), mediating lung inflammation and tissue damage. In fact, evidence exists that Th2 mediators and eosinophilia are associated with worse outcomes in a subset of individuals with severe COVID-19 (Fraissé and others 2020; Lucas and others 2020).

Furthermore, histopathological analyses of postmortem lung specimens have confirmed that COVID-19 differs from influenza by a robust Th2 response that accompanies local Th1 and Th17 inflammation in some fatal cases (Vaz de Paula and others 2020; Choreño-Parra and others 2021a). These deleterious effects of Th2 responses could also initiate pathogenic processes that favor the progression to pulmonary fibrosis, as observed in several severe COVID-19 patients discharged from hospitals (Mo and others 2020).

Considering the evidence, we propose that the optimal immune therapeutics for COVID-19 should not only block specific immune signaling pathways associated with hyperinflammation but also reestablish a convenient immune balance that promotes protective immunity in the specific subgroup of patients who display polyfunctional cytokine production. For this purpose, some cytokines could be targeted. For instance, monoclonal antibodies against IL-4 (dupilumab) have been used in patients with atopic dermatitis and COVID-19 without increasing the risk of severe complications and even apparently reducing respiratory symptoms (Caroppo and others 2020; Carugno and others 2020; Ferrucci and others 2020; Ungar and others 2022). IL-9 and TSLP could be other targets to inhibit Th2 responses in COVID-19 patients, as these molecules promote allergic inflammation (Temann and others 2002; Ito and others 2012; Koch and others 2017). Monoclonal antibodies against IL-9 (MEDI-528) and TSLP (tezepelumab) are currently in clinical trials for asthma.

Although MEDI-528 inhibits several aspects of the immunopathology of asthma in mice, clinical data are yet scarce (Gong and others 2017). Conversely, tezepelumab improves lung function and reduces eosinophilia and exacerbations in patients with uncontrolled asthma (Menzies-Gow and others 2021). Hence, future studies should assess whether tezepelumab could improve outcomes in COVID-19.

Concluding Remarks

The data summarized in this article reveal important similarities and differences in the immune profile of severe influenza and COVID-19. These diseases display increased levels of cytokines with anti-viral (IFN-α, IFN-β), inflammatory (TNFα, IL-12, IL-22), regulatory (IL-10), chemoattractant (CXCL8, CCL2, CCL4, CCL5, CXCL9, CXCL10), angiogenic (FGF, PDGF, PDGF), and growth factor (G-CSF, FGF, PDGF) properties. Hence, pathogenic mechanisms such as excessive innate immune activation, monocyte/neutrophil chemotaxis, and microvascular dysfunction might be important during the 2 diseases. Conversely, discrepancies in the immune signature of these infections include higher levels of Th1 cytokines along with IL-2, APRIL, sTNF-R1, sTNF-R2, SP-D, and CXCL17 in severe influenza patients, with COVID-19 displaying a polyfunctional Th1/Th2/Th17 immune activation profile in some patients with severe manifestations. Hence, reestablishing a balanced immune reaction might be a good objective for host-directed therapies directed to certain subgroups of COVID-19 patients.

Nonetheless, additional research is warranted to validate these immune profiles and clarify the best timing for administering specific immunotherapies according to the cytokine dynamics of these infections.

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Authors' Contributions

Design of the study: J .A.C.-P. and J.Z. Searching for literature: L.M.P.-H., J.A.R.-N., I.A.G.-G., S.I.-C., and J.A.C.-P. Summarizing information: L.M.P.-H., J.A.R.-N., I.A.G.-G., S.I.-C., and J.A.C.-P. Drafting the article: I.A.G.-G., S.I.-C., L.M.P.-H., J.A.R.-N., and J.A.C.-P. Curating the article: J.Z. and J.A.C.-P. Figures: L.M.P.-H., J.A.R.-N., I.A.G.-G., and S.I.-C. All the authors read and approved the final version of the article.

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