Aberrant Cytokine Activity in the Host Immune Response to COVID-19 Leads to Cytokine Release Syndrome

By Kenneth Oh

Emerging medical reports from the COVID-19 pandemic include a broad spectrum of patient symptoms due to the host immune response. Host cells utilize cytokines and chemokines to coordinate nearly all aspects of an immunogenic response to pathogens: acute inflammation, innate response, and adaptive immunity. Evidence increasingly suggests that cytokine release syndrome (CRS, or cytokine storm), a type of exuberant immune response, may be responsible for severe complications, including acute respiratory distress syndrome (ARDS) and death, as well as many of the milder symptoms observed.

As of May 7, 2020, there were more than 3.7 million confirmed cases of, and over 264,000 deaths from, COVID-19 disease worldwide (Johns Hopkins University COVID-19 Dashboard, coronavirus.jhu.edu/map.html). While many scientists race to perform virological assessments of the SARS-CoV-2 virion, others are focusing on the host immune response, given the range of host responses in the context of comorbidities, complications, and causes of death from COVID-19. In a meta-analysis of 5,700 hospital-admitted patients from the New York area, the most common comorbidities were hypertension (n = 3,026; 56.6%), obesity (n = 1,737; 41.7%), and diabetes (n = 1,808; 33.8%) (Richardson et al. 2020). All three of the most prevalent comorbidities in patients with COVID-19 are associated with chronic high- or low-grade inflammation (Bartoloni et al. 2017; Ellulu et al. 2017; Tsalamandris et al. 2019). Chronic inflammation is a physiological state of elevated circulating proinflammatory cytokines due to one or multiple preexisting conditions (comorbidities), a prior or current infection, or both.

A serious complication from COVID-19, which results in severe illness or death, is ARDS. ARDS is the condition of hypoxemia (low blood oxygen) and results in a rapid onset of respiratory failure. ARDS can be caused by a variety of mechanisms. Beginning with an acute inflammatory phase, a macrophage- or infected-cell–driven proinflammatory cytokine mediation (IL-1, IL-1β, IL-6, IL-8, and TNF-α) acts locally to activate neutrophils and trigger perforation at the alveoli, resulting in a buildup of mucosal and endemic fluids and cellular debris. This strong proinflammatory response is controlled by anti-inflammatory cytokines, such as macrophage inhibitory factor (MIF), IL-10, and IL-11. However, if immunological homeostasis is not achieved, counterproductive fibrotic lung repair takes place, and the alveolar space becomes filled with stem cells and new blood vessels (the “ground-glass” effect), leading to poor oxygen uptake and often resulting in death. A recent evaluation of 150 patients from Wuhan, China lists respiratory failure as a result of ARDS as the leading cause of death from COVID-19 (Ruan et al. 2020).

As our understanding of the pathophysiology of COVID-19 has evolved, a host immune hyperinflammatory response has been implicated as a major contributor to severe illness, poor outcomes, and death. CRS is the aberrant overproduction of proinflammatory cytokines, such as IFN-γ, IL-1α, IL-1β, IL-6, IL-8, GM-CSF, M-CSF, and TNF-α (Tisoncik et al. 2012), resulting in high concentrations of systemic circulating cytokines. At the onset of viral infection, an acute inflammatory event is triggered by foreign pattern recognition receptors, which recruit other immune cells to destroy the foreign pathogen while simultaneously inflicting localized collateral damage. In an ideally functioning immune response, a reparative process is initiated shortly thereafter, and homeostasis is achieved through anti-inflammatory cytokines and host tissue repair (primarily by endothelial cells).

However, excess proinflammatory cytokines may be present due to a hyperinflammatory response to a virulent pathogen; preexisting circulating cytokines, chemokines, and their cognate soluble receptors (chronic, low-grade, or high-grade inflammation); or both. When coupled with inflammation-induced vascular leakage, an influx of proinflammatory

cytokines into the circulatory system results, inducing systemic inflammation and tissue damage. Complications, such as cardiac injury or arrest, sepsis, ARDS, lung injury, organ failure, encephalopathy, and death — all of which have been observed in hospitalized patients with COVID-19 (Jiang et al. 2020; Zeng et al. 2020; Poyiadji et al. 2020; Filatov et al. 2020) — may result.

CRS is often not listed as a clinical cause of death, in part because an exact definition does not yet exist, and partly because the formal clinical classification schemes rely mainly on physiological qualitative characterization and the presence of general inflammation markers, such as C-reactive protein. However, studies of COVID-19 pathophysiology have increasingly implicated CRS as a root cause or underlying factor in COVID-19–related deaths and a serious result of immune system dysregulation that warrants significantly more research. CRS is also a major concern and is considered a high-risk factor in treatment with advanced forms of T-cell–recruiting therapies, such as chimeric antigen receptor T-cell therapy (Garcia Borrega et al. 2019). Therefore, the pathophysiologies of CRS, ARDS, and chronic inflammation merit much more investigation.

Proinflammatory cytokines, such as IFN-γ, IL-1β, IL-6, IL-8, GM-CSF, M-CSF, and TNF-α, have received significant attention in CRS and ARDS research (Figure 1). Furthermore, proinflammatory cytokines are often investigated in relation to both CRS and ARDS, as these two diseases share similar pathologies, although the exact causal relationship is still under investigation. Many noncanonical cytokines warrant more research as well, as their role in immune response and regulation is critical.

One of the first reports emerging from the epicenter of the SARS-CoV-2 outbreak in Wuhan, China measured cytokine levels in hospitalized patients with COVID-19 using the Bio-Rad Bio-Plex Pro Human Cytokine 27-Plex Assay (see Table 1 for assay composition). The researchers reported higher plasma concentrations for IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, FGF basic, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, TNF-α, and VEGF in both ICU patients and non-ICU patients than in healthy adults. Higher plasma concentrations of IL-6 were found in patients in ICU only. Notably, further comparisons indicated higher levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNF-α in ICU patients than in non-ICU patients (Huang et al. 2020).

In another report, researchers performed a longitudinal study (three time points over 15+ days) measuring the plasma cytokine and chemokine levels of twelve patients with COVID-19, eight patients with bacterial pneumonia, eight patients with influenza virus A H7N9, and eight healthy subjects in Shenzhen, China using the Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex. The composition of this panel and two other Bio-Rad human cytokine and chemokine panels is described in Table 1. Their analysis revealed significant elevations in 38 of the 48 cytokines and chemokines measured in patients with COVID-19. Further analysis revealed a constellation of 17 cytokines linked to SARS-CoV-2 virion load and 15 cytokines strongly associated with Murray lung injury score, which could predict disease severity according to receiver operating characteristic (ROC) and ROC/area under the ROC curve (ROC/AUC) curves for COVID-19 (Liu et al. 2020).

As the need to emerge from this global pandemic grows, performing more research on host immune responses by evaluating multiple cytokines (ideally in longitudinal studies) is essential and urgently needed in order to understand the pathophysiology of COVID-19 and the underlying mechanisms of CRS.

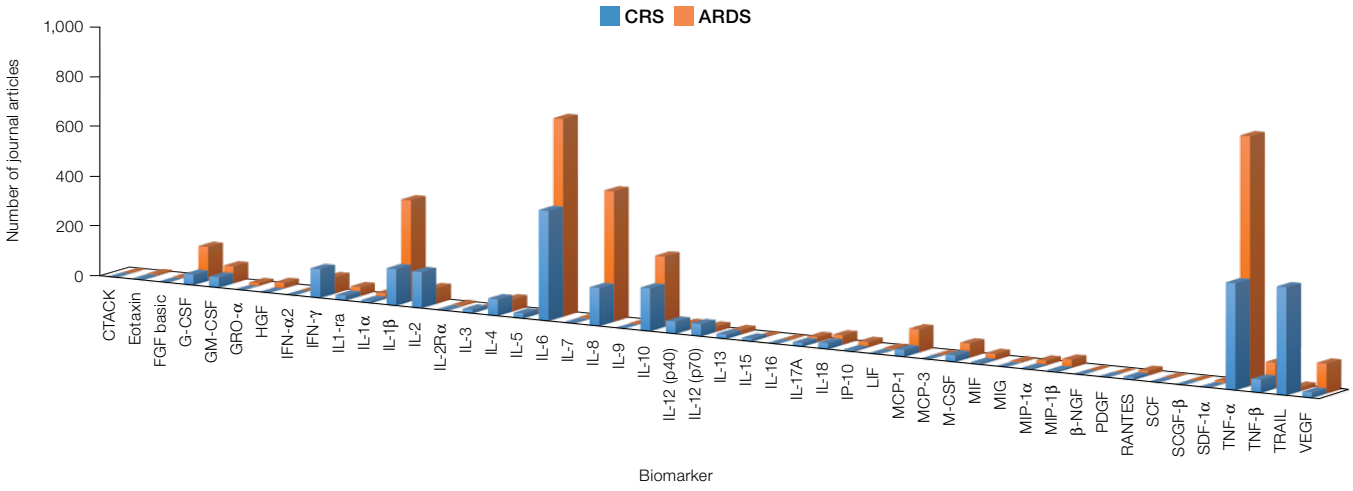

Fig. 1. Number of publications associating cytokine and chemokine biomarkers with CRS and ARDS between 1990 and April 2020, according to a PubMed search. Blue bars, publications referencing CRS. Orange bars, publications referencing ARDS.

Table 1. The composition of three human cytokine and chemokine panels.

Cytokine or Chemokine	Alternate Cytokine or Chemokine Designation	Bio-Plex Pro Human Cytokine Screening 48-Plex Panel	Bio-Plex Pro Human Cytokine 27-Plex Assay	Bio-Plex Pro Human Immunotherapy 20-Plex Panel
CTACK	CCL27	✓	—	—
Eotaxin	CCL11	✓	✓	—
FGF basic	FGF-β	✓	✓	—
G-CSF	GCSF; CSF3	✓	✓	—
GM-CSF	CSF2	✓	✓	✓
GRO-α	CXCL1	✓	—	—
HGF	Hepatocyte growth factor; scatter factor (SF)	✓	—	—
IFN-α2	IFN-a2	✓	—	—
IFN-γ	—	✓	✓	✓
IL-1Rα	IL-1Ra	✓	✓	—
IL-1α	IL-1a; hematopoietin 1	✓	—	—
IL-1β	IL-1b; leukocytic pyrogen	✓	✓	—
IL-2	—	✓	✓	✓
IL-2Rα	CD25	✓	—	—
IL-3	Colony-stimulating factor	✓	—	—
IL-4	—	✓	✓	✓
IL-5	—	✓	✓	✓
IL-6	—	✓	✓	✓
IL-7	—	✓	✓	✓
IL-8	CXCL8	✓	✓	✓
IL-9	—	✓	✓	—
IL-10	CSIF	✓	✓	✓
IL-12 (p40)	NKSF	✓	—	—
IL-12 (p70)	NKSF1	✓	✓	—
IL-13	—	✓	✓	✓
IL-15	—	✓	✓	✓
IL-16	—	✓	—	—
IL-17A	—	✓	✓	✓
IL-18	IFN-γ inducing factor	✓	—	✓
IP-10	CXCL10	✓	✓	✓
LIF	Leukemia inhibitory factor	✓	—	—
M-CSF	Macrophage colony-stimulating factor 1	✓	—	—
MCP-1	CCL2; MCAF	✓	✓	✓
MCP-3	CCL7	✓	—	—
MIF	MMIF; GIF	✓	—	—
MIG	CXCL9	✓	—	✓
MIP-1α	CCL3	✓	✓	✓
MIP-1β	CCL4	✓	✓	✓
β-NGF	Nerve growth factor, beta	✓	—	—
PDGF-BB	Platelet derived growth factor	✓	✓	—
RANTES	CCL5	✓	✓	✓
SCF	Stem cell factor; steel factor	✓	—	—
SCGF-β	Stem cell growth factor, beta	✓	—	—
SDF-1α	CXCL12; stromal cell–derived factor 1	✓	—	—
TNF-α	Cachexin; cachectin; DIF; TNFSF2	✓	✓	✓
TNF-β	Lymphotoxin-α	✓	—	—
TRAIL	TNFSF11	✓	—	—
VEGF	—	✓	✓	—

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