Macrophage Responses Associated with COVID-19:

A Pharmacological Perspective

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Abstract

COVID-19 has caused worldwide death and economic destruction. The pandemic is the result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has demonstrated high rates of infectivity leading to great morbidity and mortality in vulnerable populations. At present, scientists are exploring various approaches to curb this pandemic and alleviate its health consequences, while racing to develop a vaccine. A particularly insidious aspect of COVID-19 is the delayed overactivation of the body's immune system that is manifested as the cytokine storm. This unbridled production of pro-inflammatory cytokines and chemokines can directly or indirectly cause massive organ damage and failure. Systemic vascular endothelial inflammation and thrombocytopenia are potential consequences as well. In the case of COVID-19, the cytokine storm often fits the pattern of the macrophage activation syndrome with lymphocytopenia. The basis for the imbalance between the innate and adaptive immune systems is not clearly defined, but highlights the effect of SARS-CoV-2 on macrophages. Here we discuss the potential underlying basis for the impact of SARS-CoV-2 on macrophages, both direct and indirect, and potential therapeutic targets. These include granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 6 (IL-6), interferons, and CXCL10 (IP-10). Various biopharmaceuticals are being repurposed to target the cytokine storm in COVID-19 patients. In addition, we discuss the rationale for activating the macrophage alpha 7 nicotinic receptors as a therapeutic target. A better understanding of the molecular consequences of SARS-CoV-2 infection of macrophages could lead to novel and more effective treatments for COVID-19.

Key words: Immunopharmacology, immunomodulation therapy, pandemic, cytokine storm, macrophage activation syndrome, biologicals.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December of 2019 and quickly wreaked havoc around the world in the form of the pandemic COVID-19, causing death, undermining economies, overwhelming medical professionals, and challenging the scientific community (Liu et al., 2020b). This positive-sense single-stranded RNA virus has proven to be highly contagious, being spread by symptomatic and likely asymptomatic individuals (Furukawa et al., 2020; Huff and Singh, 2020; Oran and Topol, 2020). As the name suggests, the primary target of SARS-CoV-2 is the lungs, but other organs such as blood vessels, heart, and brain are susceptible as well. All age groups are vulnerable to infection, but generally exhibit different degrees or classes of symptoms, with those over 60, male, and with underlying medical conditions more likely to exhibit severe symptoms and succumb to viral toxicity (Conti and Younes, 2020; Team, 2020). Some 81% exhibit mild, moderate, or no symptoms; 14% show severe symptoms; and 5% experience critical disease with high mortality (Wu and McGoogan, 2020). An especially alarming complication of COVID-19 is the cytokine storm that develops after a week or two of delay in severely infected individuals.

SARS-CoV-2 has 4 structural proteins, namely the E (envelope), S (spike), M (membrane), and N (nucleocapsid) proteins (Guo et al., 2020). The N protein holds the RNA genome, while the S, E, and M proteins form the viral envelope. The virus primarily gains entry into a human cell by binding to the exopeptidase angiotensin converting enzyme 2 (ACE2). This protein is located on the membrane surface of several cell types including alveolar type II and endothelial cells. Proteins other than ACE2 may function as receptors for entry as well (Guo et al., 2020). Cell entry is facilitated by cleavage of the spike protein by the serine protease TMPRSS2 or a furin-like proprotein convertase, thereby exposing the fusion peptide. Besides

inducing cell death, viral infection can initiate an inflammatory response, which with SARS-CoV-2 is thought to manifest among other things as widespread vascular endothelial dysfunction (Teuwen et al., 2020). Beyond this, however, increasing evidence supports the conclusion that SARS-CoV-2 may exert some of its lethal effects by insidiously compromising the body's immune response. Here we summarize evidence for macrophages as targets of SARS-CoV-2 and the implication that has for immunomodulatory treatments of COVID-19 (Fig. 1).

2. Cytokine storm

Progression of COVID-19 in more severe cases is marked by the delayed occurrence of a cytokine storm or cytokine release syndrome, due to overactivation of the immune system. Although not definitively established, this phenomenon is thought to contribute to the acute respiratory distress syndrome (ARDS) and widespread organ damage that foretells death. Nor is it clear what relationship there is between the cytokine storm and thrombocytopenia, which is common in patients with COVID-19 and may ultimately contribute to adverse outcome, although both enhanced platelet activation/consumption and destruction are likely outcomes of the cytokine storm. Multi-organ (micro-) thrombosis seems to characterize severe COVID-19 cases (McFadyen et al., 2020; Prieto-Pérez et al., 2020), and likely reflects in part the production of pro-inflammatory cytokines, such as IL-1β and TNF-α, by macrophages (Conti et al., 2020a).

Notably, excessive activation or proliferation of macrophages is a contributing factor to hemophagocytic histiocytosis (HH) also known as secondary hemophagocytic lymphosistiocytosis (Xu et al., 2020). HH has been identified as a deregulation of the immune system, characterized by hemophagocytosis by macrophages, overactivation of cytotoxic T cells, and pro-inflammatory cytokine massive release (Ramos-Casals et al., 2014). HH is the

histological counterpart of the macrophage activation syndrome. A clinical study performed on post-mortem bone marrow samples taken from patients who died from COVID- 19 showed findings highly consistent with the diagnosis of HH (Prieto-Pérez et al., 2020). Elevated blood ferritin has also been shown to be associated with poor outcome in a retrospective study of 150 COVID-19 patients (Mehta et al., 2020a).

From multiple observations, both $CD4^+$ and especially $CD8^+$ (or cytotoxic) T-cells appear to be over-activated early-on in COVID-19 resulting in the excessive production of granulocyte-macrophage colony-stimulating factor (GM-CSF), which in turn stimulates monocytes/macrophages to produce interleukin-6 (IL-6) and other inflammatory factors. With time, there is a significant decrease in peripheral $CD4^+$ and $CD8^+$ T lymphocytes, as well as natural killer (NK cells) in COVID-19 patients, perhaps secondarily to their sustained activation by macrophage-derived interferon gamma-induced protein 10 (IP-10), also known as CXCL10. With disease progression, neutrophilia may occur, especially in those with severe critical pulmonary conditions (Liu et al., 2020a).

3. Macrophage (monocytes)

3.1 Inflammatory signature

Human monocytes and macrophages express ACE2, as well as TMPRSS2 and furin, and would seem to be a widespread target for SARS-CoV-2 infection (Abassi et al., 2020; Wang et al., 2020b). Evidence was reported in COVID-19 patients for the infection of macrophages of the spleen and lymph nodes with SARS-CoV-2, which was associated with severe lymphocyte apoptosis (Wang et al., 2020b). Moreover, infected macrophages were shown to produce IL-6, a pro-inflammatory cytokine that directly promotes lymphocyte necrosis and would explain in part

the common characteristic of lymphocytopenia in COVID-19 patients. Based on their morphology and ability to produce IL-6, TNF-α, and IL-10, as well as surface expression of CD11b, CD14, CD16, CD68, CD80, CD163, and CD206, circulating monocytes have an activated or pro-inflammatory phenotype. The expression of CD163 and CD206 suggests a bias towards the intermediate or regulatory phenotype, with CD163 expression being a feature of activated monocytes/macrophages in hemophagocytic lymphosistiocytosis syndrome (Wang et al., 2020b). An increase in the pool size of the intermediate subtype of monocytes may be characteristic of severe COVID-19 (Merad and Martin, 2020b). The activated plasma blood monocyte phenotype and lymphocytopenia would seem to persist into the recovery stage as well (Wen et al., 2020).

Multiple studies have demonstrated that the lungs are a target of macrophages in COVID-19 (Chua et al., 2020; Wang et al., 2020b). Inflammatory macrophages are increased with increased levels of nonresident macrophages, which in the upper respiratory tract have a highly inflammatory phenotype with the expression of a number of chemokines and pro-inflammatory cytokines IL-1B, IL-8, IL-18, and TNF-α (Chua et al., 2020; Liao et al., 2020). Macrophages in the lower airways were found to have an even stronger inflammatory signature and overall there was a strong correlation between activation status of non-resident macrophages and COVID-19 disease severity (Chua et al., 2020). Other immune cells, such as mast cells, likely act synergistically with macrophages to cause lung damage (Kritas et al., 2020).

3.2 Interferon suppression

Although CXCL10, as well as CCL2, are interferon (IFN)-induced genes, there is evidence for impaired or delayed Type 1 IFN signaling in SARS-CoV-2-infected cells. One ex

146 vivo experiment with lung tissue showed that SARS-CoV-2 induced less IFNs and pro-
147 inflammatory mediators than SARS-CoV (Chu et al., 2020). Single-cell RNA sequencing
148 analysis of bronchoalveolar lavage samples from severe and mild COVID-19 patients revealed
149 that SARS-CoV-2 mainly infects the epithelial and recruited inflammatory macrophage subsets
150 (Bost et al., 2020). In the latter, a disease severity-associated downregulation of type I IFN genes
151 was noted. Notably, IFN is known to exhibit multiple biological functions such as antiviral,
152 antiproliferative, and immunomodulatory effects (Nile et al., 2020; Wang et al., 2019). How
153 SARS-CoV-2 thwarts intrinsic innate immune responses in monocyte-macrophages is not
154 defined, although in monocyte-derived dendritic cells (but not macrophages) viral antagonism of
155 STAT1 phosphorylation was reported (Yang et al., 2020). In contrast, work in Vero cells,
156 indicates that SARS-CoV-2-infected cells are still responsive to type I IFN treatment unlike
157 SARS-CoV-infected cells (Lokugamage et al., 2020). Of note, ACE2 was shown to be an
158 interferon-stimulated gene in human lung cells, which is also upregulated by smoking and viral
159 infections (Smith et al., 2020). A discussion of possible means by which SARS-CoV-2 attenuates
160 the interferon response can be found elsewhere (Paces et al., 2020). Recently, it was reported
161 that the SARS-CoV-2 viral ORF6, ORF8 and N proteins were potential inhibitors of the type I
162 interferon signaling pathway (Li et al., 2020).
163 In light of these observations and urgent need to identify new therapies to control
164 COVID-19 severity, IFN approved drugs have emerged as a potential treatment for COVID-19
165 patients. For instance, it has been demonstrated that the administration of recombinant IFNs to
166 SARS-CoV and SARS-CoV-2 patients decreased viral protein synthesis and replication
167 (Falzarano et al., 2013; Li et al., 2019; Zumla et al., 2016). In agreement, a recent published
168 study on MERS-CoV patients reported that a combination of remdisevir and IFN beta showed a

superior antiviral effect when compared with lopinavir/ritonavir combination (Sheahan et al., 2020). Therefore, testing the efficacy and safety of recombinant IFNs may be a worthwhile promising approach in the setting of COVID-19. Triple antiviral therapy with lopinavir-ritonavir, ribavirin and interferon beta-1b was reported to be safe and superior to lopinavir-alone in improving symptoms and reducing viral shedding and hospitalization in those with mild to moderate COVID-19 (Hung et al., 2020). On the other hand, there is evidence that IFN might be playing an important role in COVID-19 hyper-inflammation, suggesting that timing is a consideration (Conti et al., 2020c; Lee et al., 2020). Analysis of monocytes by single-cell RNA-seq from patients with severe COVID-19 exhibited signs of a type I IFN response along with TNF/IL-1β-driven inflammation.

3.3 Possible contribution of nicotine and nicotinic acetylcholine receptors

Although multiple investigations report a detrimental impact of nicotine on COVID-19 patients through up-regulating ACE2 receptors in the lungs (Farsalinos et al., 2020a; Leung et al., 2020; Russo et al., 2020), recently published epidemiological studies reveal that smokers are either asymptomatic or show less severe respiratory symptoms compared with non-smokers (Covid et al., 2020; Farsalinos et al., 2020b; Kloc et al., 2020; Miyara et al., 2020; Petrilli et al., 2020). A disruption of the cholinergic anti-inflammatory pathway in COVID-19 patients has been noted (Farsalinos et al., 2020a; Farsalinos et al., 2020c). It has been reported that over-responsiveness of the immune system, otherwise known as the cytokine storm, highly correlates with enhanced severity of COVID-19 infection, substantially increasing the mortality rate (Wang et al., 2020a; Ye et al., 2020). In the human lungs, the inflammatory response is mainly mediated by lung macrophages with two main types: the alveolar and interstitial macrophages

(Kloc et al., 2020). Under physiological conditions, the alveolar macrophages exhibit anti-inflammatory characteristics by dampening the adaptive immune response and suppressing pro-inflammatory cytokines release (Kloc et al., 2020). Following a viral infection such as COVID-19, the alveolar macrophages switch from the anti- to pro-inflammatory phenotype, initiating consequently an inflammatory response, then switch back during the resolution phase to the anti-inflammatory phenotype, promoting thereafter tissue repair in the site of injury (Hu and CHRISTMAN, 2019; Hussell and Bell, 2014). In the context of COVID-19 infection, an accumulation of macrophages in the lungs of COVID-19 patients has been observed (Wang et al., 2020a). Besides resident macrophages, monocyte-derived and non-resident macrophages have been described in COVID-19 patients (Chua et al., 2020); however, a better understanding of their interrelationship is needed.

Of note, lung macrophages have been shown to express ACE2 receptors, facilitating therefore the entry of SARS-CoV-2 to host cells (Tsaytler et al., 2011; Verdecchia et al., 2020). Besides ACE2 receptors, lung macrophages express alpha 7 nicotinic receptors (nAChRs α7) (Abrial et al., 2012). nAChRs α7 are potentially implicated in attenuating the cytokine storm through decreasing pro-inflammatory cytokine release (Kalamida et al., 2007; Tracey, 2002). For instance, it has been indicated that activation of nAChRs α7 located on lung macrophages by acetylcholine and/or nicotine mitigates the hyper-inflammatory response mediated disease severity (Lu et al., 2014; Tindle et al., 2020). Strong evidence reveals that the cholinergic anti-inflammatory pathway mediated by nAChRs α7 inhibits the translocation of the pro-inflammatory marker NF-κB to the nucleus and activates the JAK2-STAT3 pathway, consequently suppressing the inflammatory response and decreasing the cytokine storm in the lungs (Báez-Pagán et al., 2015; Changeux et al., 2020; Lu et al., 2014). Given the observed lower

number of hospitalized COVID-19 patients among smokers, the potential role of medicinal nicotine to alleviate COVID-19 progression and development should be rapidly studied and clearly distinguished from conventional smoking that has no therapeutic effects.

3.4 Chemokine profile: a possible role for CXCL10 (IP-10)

Longitudinal profiling of 71 COVID-19 patients identified early expression of inhibitory mediators IL-10 and IL-1RA, along with the chemokine CCL5 (aka RANTES), in those with mild but not severe disease (Zhao et al., 2020). CCL5 is chemotactic for T cells, as well as eosinophils and basophil. On the other hand, the majority of cytokines associated with the cytokine storm in viral infections, including IL-6 and IFN-γ, were only increased at a late stage in severe illness, with TNF and GM-CSF not showing a difference between mild and severe cases.

Multiple studies have documented the upregulation of not only inflammatory cytokines but also chemokines in COVID-19 patients. Chemokines are low molecular weight proteins that act largely as chemoattractants for immune cell recruitment during inflammation, as well as modulators of immune cell homeostasis and angiogenesis (Coperchini et al., 2020). Compared to non-ICU patients, COVID-19 patients admitted to the ICU, exhibited higher plasma levels of IL2, IL7, IL10, GSCF, CXCL10 (IP-10), CCL2 (MCP1), CCL3 (MIP1A), and TNFα, indicating activation of T-helper 1 (Th1) cell function (Huang et al., 2020), although increased circulating levels of Th2-immune related cytokines IL-4 and IL-10 implicated in inflammation suppression are noted as well (Han et al., 2020). Transcriptomic analysis of bronchoalveolar lavage fluid of COVID-19 patients revealed an upregulation of CXCL1, CXCL2, CXCL6, CXCL8 (IL8), CXCL10 (IP-10), CCL2 (MCP-1), CCL3 (MIP-1A), and CCL4 (MIP1B) (Xiong et al., 2020).

CXCL10 (IP-10) is a chemoattractant for monocytes/macrophages, dendritic cells, NK cells, and T cells; CCL2 (MCP-1) is a chemoattractant for monocytes, dendritic cells, and memory T cells. CXCL2 and CXCL8, which are secreted by monocytes/macrophage, serve as potent chemoattractants for neutrophils. Single cell RNA sequencing of nasopharyngeal and bronchial samples from COVID-19 patients identified increased inflammatory macrophages that express CCL2, CCL3 (MIP-1A), CCL20, CXCL1, CXCL3, CXCL10 (IP-10), CXCL8 (IL8), IL1B and TNF-α (Chua et al., 2020). Levels correlated with disease severity. CXCL10 (IP-10) levels were previously associated with the severe acute respiratory syndrome (SARS) disease progression and resolution due to the SARS-CoV virus (Altara et al., 2016; Jiang et al., 2005), and development of ARDS in preclinical models (Coperchini et al., 2020). The elevated nasopharyngeal levels of CXCL10 with COVID-19 may permit this chemokine to be used in widespread immunoassay testing for early detection of SARS-CoV-2-infection (Cheemarla et al., 2020).

3.5 Possible contribution of GM-CSF

Mounting evidence suggests that immunomodulatory agents, including GM-CSF, could be a promising therapy for COVID-19 (Lang et al., 2020; Mehta et al., 2020b). GM-CSF is known to be implicated in the production of granulocytes, monocytes, macrophages, and dendritic cells from progenitor cells, a process known as myelopoiesis (Egea et al., 2010; Fleetwood et al., 2007). It has been demonstrated that GM-CSF is secreted by different cell types including alveolar type II epithelial cells, playing therefore a key role in the integrity of alveolar barriers and maturation of alveolar macrophages (Cakarova et al., 2009; Rösler and Herold, 2016). Multiple investigations have considered GM-CSF as a pivotal cytokine that activates both

the innate and adaptive immune response. For instance, GM-CSF can polarize myeloid cells into a pro-inflammatory phenotype, releasing subsequently reactive oxygen species and pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and chemokines including CCL17, CCL2, and IL8, which can attract lymphocytes, monocytes, and neutrophils to the site of inflammation (Hamilton, 2020). It has also been reported that GM-CSF can prime dendritic cells to activate T cells, boosting thereafter the immune response by enhancing the recruitment of myeloid cells to the site of injury (Cao et al., 2015; Komuczki et al., 2019; Zhang et al., 2013). Since the goal of enhancing lung tissues integrity and dampening hyper-active immune response may lead to a drastic decrease in morbidity and mortality rate in COVID-19 patients, administration of GM-CSF as a promising therapy is being clinically investigated (Lang et al., 2020). Pre-clinical investigations revealed that overexpression of GM-CSF decreased apoptosis in alveolar wall cells, consequently preventing hyperoxia-induced lung damage (Baleeiro et al., 2006; Paine III et al., 2003). A clinical study performed by Matute-Bello et al. reported that in patients ARDS, increased GM-CSF in bronchoalveolar lavage fluid was associated with decreased mortality rate through potentially improved alveolar macrophage survival (Matute-Bello et al., 2000). This observation was further strengthened with a clinical study completed by Herold et al. showing that administration of inhaled GM-CSF to patients with pneumonia-associated ARDS enhanced oxygenation and lung compliance (Herold et al., 2014). Currently, a clinical study is assessing the potential beneficial effect of using inhaled and intravenous GM-CSF agonist in respiratory failure COVID-19 patients (Movers et al.).

The potential benefits of administrating GM-CSF agonist in the context of COVID-19 patients, however, should be carefully studied, particularly in the late stage of COVID-19 where lung injury is thought to be driven by the cytokine storm rather than viral overload (Siddiqi and

Mehra, 2020). Paradoxically, considerable interest in administrating anti-GM-CSF is gaining interest in the setting of COVID-19, given that a marked increase in GM-CSF expressing natural killer, B cells, and CD^+4 and CD^+8 T cells was observed in COVID-19 ICU patients when compared to mild cases (Zhou et al., 2020). However, given the role of GM-CSF in boosting the immune response to remove pathogen and enhancing lung repair, it is important to consider that the observed increase could be a result of exacerbated COVID-19 severity and related comorbidities. The rational is that during COVID-19 infection, over-activation of myeloid cells could be a critical mediator of enhanced cytokine storm, consequently aggravating tissue damage. Therefore, anti-GM-CSF therapy may decrease the detrimental immune response, and thus exert beneficial effects (Barnes et al., 2020; Mehta et al., 2020a; Merad and Martin, 2020a), a hypothesis that was supported by a preclinical study of SARS-CoV infection animal model, showing that GM-CSF mediated the infiltration of inflammatory monocytes/ macrophages into the lungs (Channappanavar et al., 2016). Taking together, these findings suggest that GM-CSF is a key player in regulating myeloid cell induced hyper-inflammation in many tissues including the lungs. Anti-GM-CSF approach in patients with COVID-19, however, should be well monitored, given the critical contribution of GM-CSF in alveolar macrophage function and pathogen clearance.

As of the start of May 2020, there were some 49 clinical trials underway targeting the cytokine storm in COVID-19 patients (Wang et al., 2020b). The vast majority involve biologicals. Besides those involving GM-CSF, prominent among them are a number of studies involving anti-IL-6 strategies. In addition, antagonistic antibodies directed against TNF, IL-1, IL-1R, and IL-8 are being investigated for attenuating excessive immune activation and the cytokine storm (Conti et al., 2020b). The rationale behind those targeting the actions of GM-CSF

latter in COVID-19 is that this cytokine constitutes an autocrine/paracrine positive feedback loop that helps drive the cytokine storm (Mehta et al., 2020c). In a preliminary study, dexamethasone showed promise in reducing mortality of hospitalized COVID-19 patients if they were receiving respiratory support (mechanical ventilation or oxygen) (Group et al., 2020), but targeting the cytokine storm via broad-spectrum immunosuppression does raise a number of concerns (Theoharides and Conti, 2020).

3.6 Possible contribution of the renin angiotensin system

SRS-CoV-2 can gain entry into monocytes/macrophages via ACE2, although the virus is not thought to replicate in these cells. In this way, macrophages may act as a sort of "Trojan horse", allowing for the delivery of the virus to lung and other tissue parenchyma (Abassi et al., 2020). ACE2 is a protease that forms part of the beneficial counterpoint to the renin-angiotensin system (Forrester et al., 2018). By removing the carboxy-terminus amino acid, it converts the vasoconstrictive and pro-inflammatory octapeptide angiotensin II (Ang II) to Ang (1-7), which has beneficial effects including vasodilation and anti-inflammation actions via the Mas receptor.

An additional consequence of virus-mediated ACE2 loss might be increased Ang II inflammatory effects via the Ang II type 1 (AT1) receptor or diminished protective signaling via the Mas receptor (Abassi et al., 2020). Although multiple studies reported increased ACE2 expression in COVID-19 patients who are on angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) (Ferrario et al., 2005; Igase et al., 2008), recent emerging investigations suggested that ACEIs and ARBs could exert protective effects through up-regulating ACE2, modulating negatively therefore the severity of COVID-19 (Kuba et al., 2005) and reversing the marked increase in Ang II levels, decreasing consequently its deleterious

effects on the cardiopulmonary system (Danser et al., 2020; Sommerstein et al., 2020; Zheng et al., 2020). A study done by Kuba et al. showed that the administration of exogenous ACE2 to ARDS animal model substantially decreased inflammation and enhanced oxygenation (Kuba et al., 2005). Similarly, epidemiological studies revealed that ACEIs and ARBs decreased the risk of pneumonia in general population (Liu et al., 2013; Shinohara and Origasa, 2012). Therefore, investigation aimed at testing the potential beneficial or detrimental effects of ACEIs and ARBs in the context of COVID-19 is being undertaken (Buckley et al., 2020).

4. Conclusions

Substantial evidence indicates that pro-inflammatory macrophages play a critical role in the pathological consequences of COVID-19. Additional evidence is needed concerning the presence phenotype of these cells. Nor is it clear what the relationship is between SARS-CoV-2 infection and monocyte/macrophage activation status, namely whether these immune cells are simply responding to the viral infection or are hijacked by the virus to act in an uncontrolled rogue manner. Emerging evidence indicates that targeting the cytokines and chemokines associated with their activation or restoring their innate immunity control may provide the means to successfully combat COVID-19.

Dedication

This manuscript is dedicated to G. Warren and Jessie Booz, two gentle, loving, caring, and gifted individuals, and all of those wonderful and remarkable individuals who were taken from us way too soon by the COVID-19 pandemic.

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References

Abassi, Z., Knaney, Y., Karram, T., Heyman, S.N., 2020. The Lung Macrophage in SARS-CoV-2 Infection: A Friend or a Foe? Front Immunol 11, 1312. doi: 10.3389/fimmu.2020.01312.

Abrial, C., Delyle, S.G., Buenestado, A., Naline, E., Papke, R., Devillier, P., 2012. Role of nicotinic receptors in the regulation of cytokines production by human lung macrophages. Eur Respiratory Soc.

Altara, R., Manca, M., Brandao, R.D., Zeidan, A., Booz, G.W., Zouein, F.A., 2016. Emerging importance of chemokine receptor CXCR3 and its ligands in cardiovascular diseases. Clin Sci (Lond) 130, 463-478. doi: 10.1042/CS20150666.

Báez-Pagán, C.A., Delgado-Vélez, M., Lasalde-Dominicci, J.A., 2015. Activation of the macrophage α7 nicotinic acetylcholine receptor and control of inflammation. Journal of Neuroimmune Pharmacology 10, 468-476. doi:

Baleeiro, C.E., Christensen, P.J., Morris, S.B., Mendez, M.P., Wilcoxen, S.E., Paine III, R., 2006. GM-CSF and the impaired pulmonary innate immune response following hyperoxic stress. American Journal of Physiology-Lung Cellular and Molecular Physiology 291, L1246-L1255. doi:

Barnes, B.J., Adrover, J.M., Baxter-Stoltzfus, A., Borczuk, A., Cools-Lartigue, J., Crawford, J.M., Daßler-Plenker, J., Guerci, P., Huynh, C., Knight, J.S., 2020. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. Journal of Experimental Medicine 217. doi:

Bost, P., Giladi, A., Liu, Y., Bendjelal, Y., Xu, G., David, E., Blecher-Gonen, R., Cohen, M., Medaglia, C., Li, H., Deczkowska, A., Zhang, S., Schwikowski, B., Zhang, Z., Amit, I.,

2020. Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients. Cell 181, 1475-1488 e1412. doi: 10.1016/j.cell.2020.05.006.

Buckley, L.F., Cheng, J.W.M., Desai, A., 2020. Cardiovascular Pharmacology in the Time of COVID-19: A Focus on Angiotensin-Converting Enzyme 2. J Cardiovasc Pharmacol 75, 526-529. doi: 10.1097/FJC.0000000000000840.

Cakarova, L., Marsh, L.M., Wilhelm, J., Mayer, K., Grimminger, F., Seeger, W., Lohmeyer, J., Herold, S., 2009. Macrophage tumor necrosis factor-α induces epithelial expression of granulocyte–macrophage colony-stimulating factor: impact on alveolar epithelial repair. American journal of respiratory and critical care medicine 180, 521-532. doi:

Cao, Y., Goods, B.A., Raddassi, K., Nepom, G.T., Kwok, W.W., Love, J.C., Hafler, D.A., 2015. Functional inflammatory profiles distinguish myelin-reactive T cells from patients with multiple sclerosis. Science translational medicine 7, 287ra274-287ra274. doi:

Changeux, J.-P., Amoura, Z., Rey, F.A., Miyara, M., 2020. A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. Comptes Rendus. Biologies 343, 33-39. doi:

Channappanavar, R., Fehr, A.R., Vijay, R., Mack, M., Zhao, J., Meyerholz, D.K., Perlman, S., 2016. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell host & microbe 19, 181-193. doi:

Cheemarla, N.R., Brito, A.F., Fauver, J.R., Alpert, T., Vogels, C.B.F., Omer, S.B., Ko, A., Grubaugh, N.D., Landry, M.L., Foxman, E.F., 2020. Host response-based screening to identify undiagnosed cases of COVID-19 and expand testing capacity. medRxiv. doi: 10.1101/2020.06.04.20109306.

Chu, H., Chan, J.F., Wang, Y., Yuen, T.T., Chai, Y., Hou, Y., Shuai, H., Yang, D., Hu, B., Huang, X., Zhang, X., Cai, J.P., Zhou, J., Yuan, S., Kok, K.H., To, K.K., Chan, I.H., Zhang, A.J., Sit, K.Y., Au, W.K., Yuen, K.Y., 2020. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. Clin Infect Dis. doi: 10.1093/cid/ciaa410.

Chua, R.L., Lukassen, S., Trump, S., Hennig, B.P., Wendisch, D., Pott, F., Debnath, O., Thurmann, L., Kurth, F., Volker, M.T., Kazmierski, J., Timmermann, B., Twardziok, S., Schneider, S., Machleidt, F., Muller-Redetzky, H., Maier, M., Krannich, A., Schmidt, S., Balzer, F., Liebig, J., Loske, J., Suttorp, N., Eils, J., Ishaque, N., Liebert, U.G., von Kalle, C., Hocke, A., Witzenrath, M., Goffinet, C., Drosten, C., Laudi, S., Lehmann, I., Conrad, C., Sander, L.E., Eils, R., 2020. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. Nat Biotechnol. doi: 10.1038/s41587-020-0602-4.

Conti, P., Caraffa, A., Gallenga, C.E., Ross, R., Kritas, S.K., Frydas, I., Younes, A., Di Emidio, P., Ronconi, G., Toniato, E., 2020a. IL-1 induces throboxane-A2 (TxA2) in COVID-19 causing inflammation and micro-thrombi: inhibitory effect of the IL-1 receptor antagonist (IL-1Ra). J Biol Regul Homeost Agents 34. doi: 10.23812/20-34-4EDIT-65.

Conti, P., Gallenga, C.E., Tete, G., Caraffa, A., Ronconi, G., Younes, A., Toniato, E., Ross, R., Kritas, S.K., 2020b. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J Biol Regul Homeost Agents 34, 333-338. doi: 10.23812/Editorial-Conti-2.

Conti, P., Ronconi, G., Caraffa, A., Gallenga, C.E., Ross, R., Frydas, I., Kritas, S.K., 2020c. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 34, 327-331. doi: 10.23812/CONTI-E.

Conti, P., Younes, A., 2020. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents 34, 339-343. doi: 10.23812/Editorial-Conti-3.

Coperchini, F., Chiovato, L., Croce, L., Magri, F., Rotondi, M., 2020. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev 53, 25-32. doi: 10.1016/j.cytogfr.2020.05.003.

Covid, C., COVID, C., COVID, C., Chow, N., Fleming-Dutra, K., Gierke, R., Hall, A., Hughes, M., Pilishvili, T., Ritchey, M., 2020. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–March 28, 2020. Morbidity and Mortality Weekly Report 69, 382. doi:

Danser, A.H.J., Epstein, M., Batlle, D., 2020. Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. Hypertension 75, 1382-1385. doi: 10.1161/HYPERTENSIONAHA.120.15082.

Egea, L., Hirata, Y., Kagnoff, M.F., 2010. GM-CSF: a role in immune and inflammatory reactions in the intestine. Expert review of gastroenterology & hepatology 4, 723-731. doi:

Falzarano, D., de Wit, E., Martellaro, C., Callison, J., Munster, V.J., Feldmann, H., 2013. Inhibition of novel beta coronavirus replication by a combination of interferon-alpha2b and ribavirin. Sci Rep 3, 1686. doi: 10.1038/srep01686.

Farsalinos, K., Angelopoulou, A., Alexandris, N., Poulas, K., 2020a. COVID-19 and the nicotinic cholinergic system. European Respiratory Journal. doi:

Farsalinos, K., Barbouni, A., Niaura, R., 2020b. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Internal and Emergency Medicine, 1-8. doi:

Farsalinos, K., Niaura, R., Le Houezec, J., Barbouni, A., Tsatsakis, A., Kouretas, D., Vantarakis, A., Poulas, K., 2020c. Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. Toxicology Reports. doi:

Ferrario, C.M., Jessup, J., Chappell, M.C., Averill, D.B., Brosnihan, K.B., Tallant, E.A., Diz, D.I., Gallagher, P.E., 2005. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111, 2605-2610. doi: 10.1161/CIRCULATIONAHA.104.510461.

Fleetwood, A.J., Lawrence, T., Hamilton, J.A., Cook, A.D., 2007. Granulocyte-macrophage colony-stimulating factor (CSF) and macrophage CSF-dependent macrophage phenotypes display differences in cytokine profiles and transcription factor activities: implications for CSF blockade in inflammation. The Journal of immunology 178, 5245-5252. doi:

Forrester, S.J., Booz, G.W., Sigmund, C.D., Coffman, T.M., Kawai, T., Rizzo, V., Scalia, R., Eguchi, S., 2018. Angiotensin II Signal Transduction: An Update on Mechanisms of

474 Physiology and Pathophysiology. Physiol Rev 98, 1627-1738. doi:
475 10.1152/physrev.00038.2017.
476 Furukawa, N.W., Brooks, J.T., Sobel, J., 2020. Evidence Supporting Transmission of Severe
477 Acute Respiratory Syndrome Coronavirus 2 While Presymptomatic or Asymptomatic.
478 Emerg Infect Dis 26. doi: 10.3201/eid2607.201595.
479 Group, R.C., Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., Linsell, L., Staplin,
480 N., Brightling, C., Ustianowski, A., Elmahi, E., Prudon, B., Green, C., Felton, T.,
481 Chadwick, D., Rege, K., Fegan, C., Chappell, L.C., Faust, S.N., Jaki, T., Jeffery, K.,
482 Montgomery, A., Rowan, K., Juszczak, E., Baillie, J.K., Haynes, R., Landray, M.J., 2020.
483 Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J
484 Med. doi: 10.1056/NEJMoa2021436.
485 Guo, G., Ye, L., Pan, K., Chen, Y., Xing, D., Yan, K., Chen, Z., Ding, N., Li, W., Huang, H.,
486 Zhang, L., Li, X., Xue, X., 2020. New Insights of Emerging SARS-CoV-2:
487 Epidemiology, Etiology, Clinical Features, Clinical Treatment, and Prevention. Front
488 Cell Dev Biol 8, 410. doi: 10.3389/fcell.2020.00410.
489 Hamilton, J.A., 2020. GM-CSF in inflammation. The Journal of experimental medicine 217. doi:
490 Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., Zhang, P., Liu, X., Gao, G., Liu, F., Jiang,
491 Y., Cheng, X., Zhu, C., Xia, Y., 2020. Profiling serum cytokines in COVID-19 patients
492 reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 9, 1123-
493 1130. doi: 10.1080/22221751.2020.1770129.
494 Herold, S., Hoegner, K., Vadász, I., Gessler, T., Wilhelm, J., Mayer, K., Morty, R.E., Walmrath,
495 H.-D., Seeger, W., Lohmeyer, J., 2014. Inhaled granulocyte/macrophage Colony–

stimulating factor as treatment of pneumonia-associated acute respiratory distress syndrome. American journal of respiratory and critical care medicine 189, 609-611. doi:

Hu, G., CHRISTMAN, J.W., 2019. Alveolar Macrophages in Lung Inflammation and Resolution. Frontiers in immunology 10, 2275. doi:

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497-506. doi: 10.1016/S0140-6736(20)30183-5.

Huff, H.V., Singh, A., 2020. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies. Clin Infect Dis. doi: 10.1093/cid/ciaa654.

Hung, I.F., Lung, K.C., Tso, E.Y., Liu, R., Chung, T.W., Chu, M.Y., Ng, Y.Y., Lo, J., Chan, J., Tam, A.R., Shum, H.P., Chan, V., Wu, A.K., Sin, K.M., Leung, W.S., Law, W.L., Lung, D.C., Sin, S., Yeung, P., Yip, C.C., Zhang, R.R., Fung, A.Y., Yan, E.Y., Leung, K.H., Ip, J.D., Chu, A.W., Chan, W.M., Ng, A.C., Lee, R., Fung, K., Yeung, A., Wu, T.C., Chan, J.W., Yan, W.W., Chan, W.M., Chan, J.F., Lie, A.K., Tsang, O.T., Cheng, V.C., Que, T.L., Lau, C.S., Chan, K.H., To, K.K., Yuen, K.Y., 2020. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 395, 1695-1704. doi: 10.1016/S0140-6736(20)31042-4.

Hussell, T., Bell, T.J., 2014. Alveolar macrophages: plasticity in a tissue-specific context. Nature reviews immunology 14, 81-93. doi:

Igase, M., Kohara, K., Nagai, T., Miki, T., Ferrario, C.M., 2008. Increased expression of angiotensin converting enzyme 2 in conjunction with reduction of neointima by angiotensin II type 1 receptor blockade. Hypertens Res 31, 553-559. doi: 10.1291/hypres.31.553.

Jiang, Y., Xu, J., Zhou, C., Wu, Z., Zhong, S., Liu, J., Luo, W., Chen, T., Qin, Q., Deng, P., 2005. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. Am J Respir Crit Care Med 171, 850-857. doi: 10.1164/rccm.200407-857OC.

Kalamida, D., Poulas, K., Avramopoulou, V., Fostieri, E., Lagoumintzis, G., Lazaridis, K., Sideri, A., Zouridakis, M., Tzartos, S.J., 2007. Muscle and neuronal nicotinic acetylcholine receptors. The FEBS journal 274, 3799-3845. doi:

Kloc, M., Ghobrial, R.M., Kubiak, J.Z., 2020. How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection? Immunology Letters. doi:

Komuczki, J., Tuzlak, S., Friebel, E., Hartwig, T., Spath, S., Rosenstiel, P., Waisman, A., Opitz, L., Oukka, M., Schreiner, B., 2019. Fate-mapping of GM-CSF expression identifies a discrete subset of inflammation-driving T helper cells regulated by cytokines IL-23 and IL-1β. Immunity 50, 1289-1304. e1286. doi:

Kritas, S.K., Ronconi, G., Caraffa, A., Gallenga, C.E., Ross, R., Conti, P., 2020. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. J Biol Regul Homeost Agents 34, 9-14. doi: 10.23812/20-Editorial-Kritas.

Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L., Zhang, B., Liu, G., Wang, Z., Chappell, M., Liu, Y., Zheng, D., Leibbrandt, A., Wada, T., Slutsky, A.S., Liu, D., Qin, C., Jiang, C., Penninger, J.M., 2005. A crucial

role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11, 875-879. doi: 10.1038/nm1267.

Lang, F.M., Lee, K.M.-C., Teijaro, J.R., Becher, B., Hamilton, J.A., 2020. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. Nature Reviews Immunology, 1-8. doi:

Lee, J.S., Park, S., Jeong, H.W., Ahn, J.Y., Choi, S.J., Lee, H., Choi, B., Nam, S.K., Sa, M., Kwon, J.S., Jeong, S.J., Lee, H.K., Park, S.H., Park, S.H., Choi, J.Y., Kim, S.H., Jung, I., Shin, E.C., 2020. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. Sci Immunol 5. doi: 10.1126/sciimmunol.abd1554.

Leung, J.M., Yang, C.X., Sin, D.D., 2020. COVID-19 and Nicotine as a Mediator of ACE-2. European Respiratory Journal 55. doi:

Li, C.C., Wang, X.J., Wang, H.R., 2019. Repurposing host-based therapeutics to control coronavirus and influenza virus. Drug Discov Today 24, 726-736. doi: 10.1016/j.drudis.2019.01.018.

Li, J.Y., Liao, C.H., Wang, Q., Tan, Y.J., Luo, R., Qiu, Y., Ge, X.Y., 2020. The ORF6, ORF8 and nucleocapsid proteins of SARS-CoV-2 inhibit type I interferon signaling pathway. Virus Res 286, 198074. doi: 10.1016/j.virusres.2020.198074.

Liao, M., Liu, Y., Yuan, J., Wen, Y., Xu, G., Zhao, J., Cheng, L., Li, J., Wang, X., Wang, F., Liu, L., Amit, I., Zhang, S., Zhang, Z., 2020. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med 26, 842-844. doi: 10.1038/s41591-020-0901-9.

563 Liu, C.L., Shau, W.Y., Chang, C.H., Wu, C.S., Lai, M.S., 2013. Pneumonia risk and use of
564 angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. J
565 Epidemiol 23, 344-350. doi: 10.2188/jea.je20120112.
566 Liu, X., Zhang, R., He, G., 2020a. Hematological findings in coronavirus disease 2019:
567 indications of progression of disease. Ann Hematol 99, 1421-1428. doi: 10.1007/s00277-
568 020-04103-5.
569 Liu, Y.C., Kuo, R.L., Shih, S.R., 2020b. COVID-19: The first documented coronavirus
570 pandemic in history. Biomed J. doi: 10.1016/j.bj.2020.04.007.
571 Lokugamage, K.G., Hage, A., Schindewolf, C., Rajsbaum, R., Menachery, V.D., 2020. SARS-
572 CoV-2 is sensitive to type I interferon pretreatment. bioRxiv. doi:
573 10.1101/2020.03.07.982264.
574 Lu, B., Kwan, K., Levine, Y.A., Olofsson, P.S., Yang, H., Li, J., Joshi, S., Wang, H., Andersson,
575 U., Chavan, S.S., 2014. α7 nicotinic acetylcholine receptor signaling inhibits
576 inflammasome activation by preventing mitochondrial DNA release. Molecular medicine
577 20, 350-358. doi:
578 Matute-Bello, G., Liles, C.W., Frank Radella, I., Steinberg, K.P., Ruzinski, J.T., Hudson, L.D.,
579 Martin, T.R., 2000. Modulation of neutrophil apoptosis by granulocyte colony-
580 stimulating factor and granulocyte/macrophage colony-stimulating factor during the
581 course of acute respiratory distress syndrome. Critical care medicine 28, 1-7. doi:
582 McFadyen, J.D., Stevens, H., Peter, K., 2020. The Emerging Threat of (Micro)Thrombosis in
583 COVID-19 and Its Therapeutic Implications. Circ Res. doi:
584 10.1161/CIRCRESAHA.120.317447.

585 Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., Manson, J.J., Hlh Across
586 Speciality Collaboration, U.K., 2020a. COVID-19: consider cytokine storm syndromes
587 and immunosuppression. Lancet 395, 1033-1034. doi: 10.1016/S0140-6736(20)30628-0.
588 Mehta, P., Porter, J.C., Manson, J.J., Isaacs, J.D., Openshaw, P.J., McInnes, I.B., Summers, C.,
589 Chambers, R.C., 2020b. Therapeutic blockade of granulocyte macrophage colony-
590 stimulating factor in COVID-19-associated hyperinflammation: challenges and
591 opportunities. The Lancet Respiratory Medicine. doi:
592 Mehta, P., Porter, J.C., Manson, J.J., Isaacs, J.D., Openshaw, P.J.M., McInnes, I.B., Summers,
593 C., Chambers, R.C., 2020c. Therapeutic blockade of granulocyte macrophage colony-
594 stimulating factor in COVID-19-associated hyperinflammation: challenges and
595 opportunities. Lancet Respir Med. doi: 10.1016/S2213-2600(20)30267-8.
596 Merad, M., Martin, J.C., 2020a. Pathological inflammation in patients with COVID-19: a key
597 role for monocytes and macrophages. Nature Reviews Immunology, 1-8. doi:
598 Merad, M., Martin, J.C., 2020b. Pathological inflammation in patients with COVID-19: a key
599 role for monocytes and macrophages. Nat Rev Immunol 20, 355-362. doi:
600 10.1038/s41577-020-0331-4.
601 Miyara, M., Tubach, F., Pourcher, V., Morelot-Panzini, C., Pernet, J., Haroche, J., 2020. Low
602 incidence of daily active tobacco smoking in patients with symptomatic COVID-19.
603 Qeios. doi:
604 Movers, M., Live, D.J., Finder, S., Live, N., Live, C., Live, C., Live, C., Index, U.D., Finder, E.,
605 Issuers, E., Partner Therapeutics Announces Initiation of Clinical Trial to Evaluate
606 Leukine® in Respiratory Illness in Patients with COVID-19 at Singapore General
607 Hospital. doi:

608 Nile, S.H., Nile, A., Qiu, J., Li, L., Jia, X., Kai, G., 2020. COVID-19: Pathogenesis, cytokine
609 storm and therapeutic potential of interferons. Cytokine Growth Factor Rev 53, 66-70.
610 doi: 10.1016/j.cytogfr.2020.05.002.
611 Oran, D.P., Topol, E.J., 2020. Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative
612 Review. Ann Intern Med. doi: 10.7326/M20-3012.
613 Paces, J., Strizova, Z., Smrz, D., Cerny, J., 2020. COVID-19 and the immune system. Physiol
614 Res. doi:
615 Paine III, R., Wilcoxen, S.E., Morris, S.B., Sartori, C., Baleeiro, C.E., Matthay, M.A.,
616 Christensen, P.J., 2003. Transgenic overexpression of granulocyte macrophage-colony
617 stimulating factor in the lung prevents hyperoxic lung injury. The American journal of
618 pathology 163, 2397-2406. doi:
619 Petrilli, C.M., Jones, S.A., Yang, J., Rajagopalan, H., O'Donnell, L.F., Chernyak, Y., Tobin, K.,
620 Cerfolio, R.J., Francois, F., Horwitz, L.I., 2020. Factors associated with hospitalization
621 and critical illness among 4,103 patients with COVID-19 disease in New York City.
622 MedRxiv. doi:
623 Prieto-Pérez, L., Fortes, J., Soto, C., Vidal-González, Á., Alonso-Riaño, M., Lafarga, M., Cortti,
624 M.J., Lazaro-Garcia, A., Pérez-Tanoira, R., Trascasa, Á., Antonio, A., Córdoba, R.,
625 Rodríguez-Pinilla, S.M., Cedeño, O., Peces-Barba, G., Fernández-Ormaechea, I., Díez
626 Medrano, M.J., López de Las Heras, M., Cabello, A., Petkova, E., Álvarez, B., Carrillo,
627 I., Silva, A.M., Castellanos, M., Calpena, S., Valverde-Monge, M., Fresneda, D., Rubio-
628 Martín, R., Cornejo, I., Astilleros Blanco de Cordova, L., de la Fuente, S., Recuero, S.,
629 Górgolas, M., Piris, M.A., 2020. Histiocytic hyperplasia with hemophagocytosis and

acute alveolar damage in COVID-19 infection. Mod Pathol. doi: 10.1038/s41379-020-0613-1.

Ramos-Casals, M., Brito-Zeron, P., Lopez-Guillermo, A., Khamashta, M.A., Bosch, X., 2014. Adult haemophagocytic syndrome. Lancet 383, 1503-1516. doi: 10.1016/S0140-6736(13)61048-X.

Rösler, B., Herold, S., 2016. Lung epithelial GM-CSF improves host defense function and epithelial repair in influenza virus pneumonia—a new therapeutic strategy? Molecular and cellular pediatrics 3, 29. doi:

Russo, P., Bonassi, S., Giacconi, R., Malavolta, M., Tomino, C., Maggi, F., 2020. COVID-19 and smoking: is nicotine the hidden link? European Respiratory Journal 55. doi:

Sheahan, T.P., Sims, A.C., Leist, S.R., Schafer, A., Won, J., Brown, A.J., Montgomery, S.A., Hogg, A., Babusis, D., Clarke, M.O., Spahn, J.E., Bauer, L., Sellers, S., Porter, D., Feng, J.Y., Cihlar, T., Jordan, R., Denison, M.R., Baric, R.S., 2020. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 11, 222. doi: 10.1038/s41467-019-13940-6.

Shinohara, Y., Origasa, H., 2012. Post-stroke pneumonia prevention by angiotensin-converting enzyme inhibitors: results of a meta-analysis of five studies in Asians. Adv Ther 29, 900-912. doi: 10.1007/s12325-012-0049-1.

Siddiqi, H.K., Mehra, M.R., 2020. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. The Journal of Heart and Lung Transplantation 39, 405. doi:

Smith, J.C., Sausville, E.L., Girish, V., Yuan, M.L., Vasudevan, A., John, K.M., Sheltzer, J.M., 2020. Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of

653 the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract. Dev Cell 53, 514-529 e513.
654 doi: 10.1016/j.devcel.2020.05.012.
655 Sommerstein, R., Kochen, M.M., Messerli, F.H., Grani, C., 2020. Coronavirus Disease 2019
656 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor
657 Blockers Have a Biphasic Effect? J Am Heart Assoc 9, e016509. doi:
658 10.1161/JAHA.120.016509.
659 Team, C.C.-R., 2020. Preliminary Estimates of the Prevalence of Selected Underlying Health
660 Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-
661 March 28, 2020. MMWR Morb Mortal Wkly Rep 69, 382-386. doi:
662 10.15585/mmwr.mm6913e2.
663 Teuwen, L.A., Geldhof, V., Pasut, A., Carmeliet, P., 2020. COVID-19: the vasculature
664 unleashed. Nat Rev Immunol. doi: 10.1038/s41577-020-0343-0.
665 Theoharides, T.C., Conti, P., 2020. Dexamethasone for COVID-19? Not so fast. J Biol Regul
666 Homeost Agents 34. doi: 10.23812/20-EDITORIAL_1-5.
667 Tindle, H.A., Newhouse, P.A., Freiberg, M.S., 2020. Beyond smoking cessation: Investigating
668 medicinal nicotine to prevent and treat COVID-19. Nicotine & Tobacco Research. doi:
669 Tracey, K.J., 2002. The inflammatory reflex. Nature 420, 853-859. doi:
670 Tsaytler, P., Harding, H.P., Ron, D., Bertolotti, A., 2011. Selective inhibition of a regulatory
671 subunit of protein phosphatase 1 restores proteostasis. Science 332, 91-94. doi:
672 Verdecchia, P., Cavallini, C., Spanevello, A., Angeli, F., 2020. The pivotal link between ACE2
673 deficiency and SARS-CoV-2 infection. European Journal of Internal Medicine. doi:

Wang, C., Xie, J., Zhao, L., Fei, X., Zhang, H., Tan, Y., Zhou, L., Liu, Z., Ren, Y., Yuan, L., 2020a. Aveolar macrophage activation and cytokine storm in the pathogenesis of severe COVID-19. doi:

Wang, J., Jiang, M., Chen, X., Montaner, L.J., 2020b. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. doi: 10.1002/JLB.3COVR0520-272R.

Wang, Y., Ding, Q., Lu, Y.C., Cao, S.Y., Liu, Q.X., Zhang, L., 2019. Interferon-stimulated gene 15 enters posttranslational modifications of p53. J Cell Physiol 234, 5507-5518. doi: 10.1002/jcp.27347.

Wen, W., Su, W., Tang, H., Le, W., Zhang, X., Zheng, Y., Liu, X., Xie, L., Li, J., Ye, J., Dong, L., Cui, X., Miao, Y., Wang, D., Dong, J., Xiao, C., Chen, W., Wang, H., 2020. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. Cell Discov 6, 31. doi: 10.1038/s41421-020-0168-9.

Wu, Z., McGoogan, J.M., 2020. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. doi: 10.1001/jama.2020.2648.

Xiong, Y., Liu, Y., Cao, L., Wang, D., Guo, M., Jiang, A., Guo, D., Hu, W., Yang, J., Tang, Z., Wu, H., Lin, Y., Zhang, M., Zhang, Q., Shi, M., Liu, Y., Zhou, Y., Lan, K., Chen, Y., 2020. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect 9, 761-770. doi: 10.1080/22221751.2020.1747363.

Xu, P., Zhou, Q., Xu, J., 2020. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 99, 1205-1208. doi: 10.1007/s00277-020-04019-0.

Yang, D., Chu, H., Hou, Y., Chai, Y., Shuai, H., Lee, A.C., Zhang, X., Wang, Y., Hu, B., Huang, X., Yuen, T.T., Cai, J.P., Zhou, J., Yuan, S., Zhang, A.J., Chan, J.F., Yuen, K.Y., 2020. Attenuated interferon and pro-inflammatory response in SARS-CoV-2-infected human dendritic cells is associated with viral antagonism of STAT1 phosphorylation. J Infect Dis. doi: 10.1093/infdis/jiaa356.

Ye, Q., Wang, B., Mao, J., 2020. Cytokine storm in COVID-19 and treatment. Journal of Infection. doi:

Zhang, J., Roberts, A., Liu, C., Ren, G., Xu, G., Zhang, L., Devadas, S., Shi, Y., 2013. A novel subset of helper T cells promotes immune responses by secreting GM-CSF. Cell Death & Differentiation 20, 1731-1741. doi:

Zhao, Y., Qin, L., Zhang, P., Li, K., Liang, L., Sun, J., Xu, B., Dai, Y., Li, X., Zhang, C., Peng, Y., Feng, Y., Li, A., Hu, Z., Xiang, H., Ogg, G., Ho, L.P., McMichael, A.J., Jin, R., Knight, J.C., Dong, T., Zhang, Y., 2020. Longitudinal COVID-19 profiling associates IL-1Ra and IL-10 with disease severity and RANTES with mild disease. JCI Insight. doi: 10.1172/jci.insight.139834.

Zheng, Y.Y., Ma, Y.T., Zhang, J.Y., Xie, X., 2020. COVID-19 and the cardiovascular system. Nat Rev Cardiol 17, 259-260. doi: 10.1038/s41569-020-0360-5.

Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., 2020. qi Y, Sun R, Tian Z, Xu X, Wei H. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev. doi:

719 Zumla, A., Chan, J.F., Azhar, E.I., Hui, D.S., Yuen, K.Y., 2016. Coronaviruses - drug discovery
720 and therapeutic options. Nat Rev Drug Discov 15, 327-347. doi: 10.1038/nrd.2015.37.
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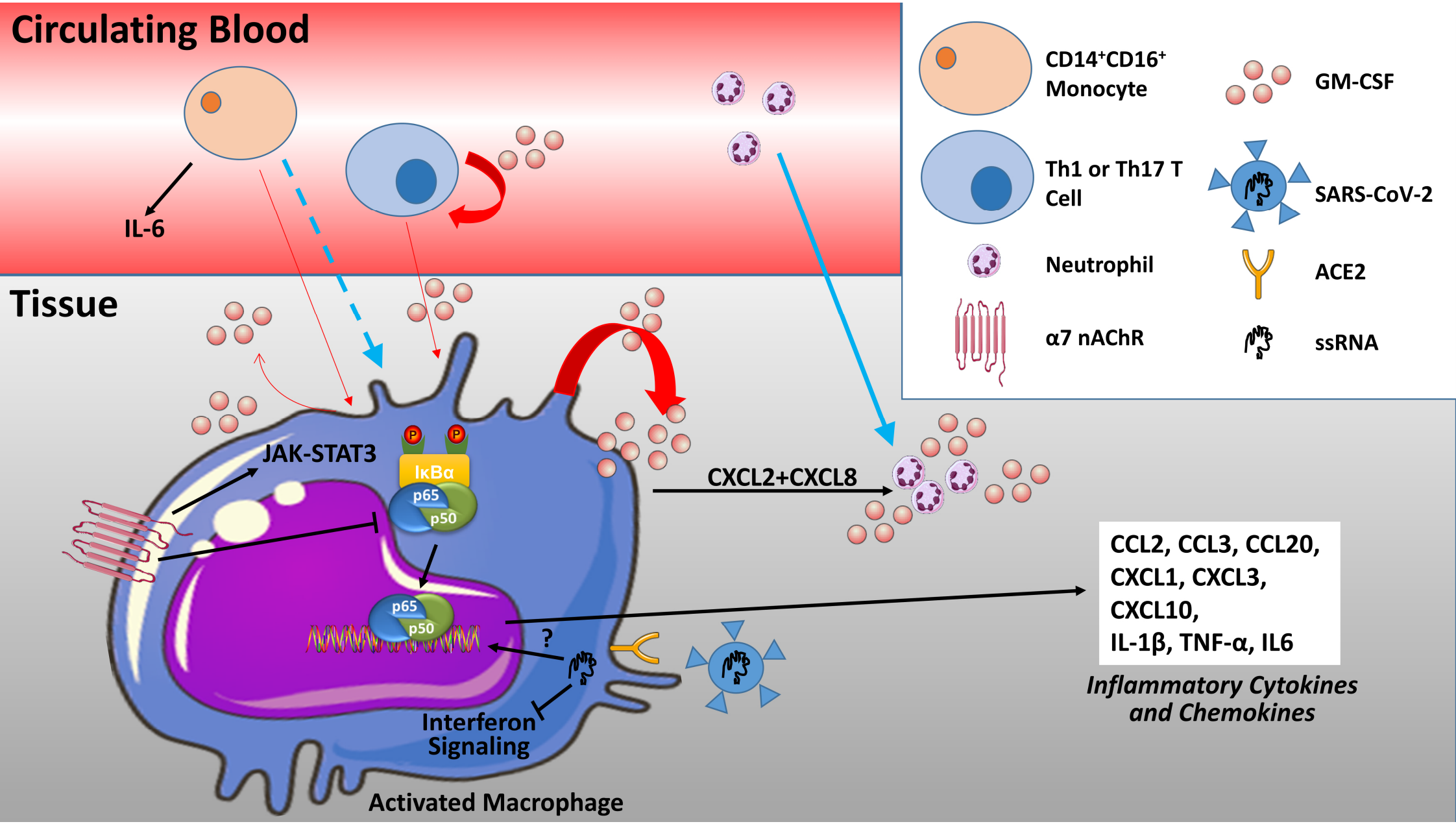
Figure Legend

Figure 1 – Macrophages at the center of the cytokine storm. With inflammation, macrophages, T cells, endothelial cells and a number of other immune and mesenchymal cells, produce the monomeric glycoprotein granulocyte-macrophage colony-stimulating factor (GM-CSF) (red arrows). Besides stimulating the production of granulocytes and monocytes, GM-CSF can serve as a chemoattractant for the migration of monocytes and neutrophils into the tissue (blue arrows), and can alter neutrophil receptors. GM-CSF signaling promotes a pro-inflammatory M1 macrophage phenotype and the production of a number of inflammatory cytokines and chemokines by monocyte-derived or tissue macrophages (black arrows). Macrophages themselves are direct targets of the SARS-CoV-2 via expression of the receptor for viral binding ACE2, as well as TMPRSS2 or a furin-like proprotein convertase. The effect of SARS-CoV-2 on macrophage phenotype is not defined, although inhibition of protective interferon signaling is reported. Lung macrophages also express the G protein-coupled alpha 7 nicotinic receptors (nAChRs α7) that signal through JAK-STAT3 and oppose inflammatory signaling by blocking the translocation of p65/p50 NF-κB into the nucleus upon IκBα (inhibitor of NF-κB) degradation. See text for additional details. Some of the content is adapted from Servier Medical Art (https://smart.servier.com/).


Circulating Blood
IL-6
Tissue
JAK-STAT3
IκBα
p65
p50
P
P
p65
p50
?
Interferon
Signaling
Activated Macrophage
CXCL2+CXCL8
CCL2, CCL3, CCL20,
CXCL1, CXCL3,
CXCL10,
IL-1β, TNF-α, IL6
Inflammatory Cytokines
and Chemokines
CD14+CD16+
Monocyte
Th1 or Th17 T
Cell
Neutrophil
α7 nAChR
GM-CSF
SARS-CoV-2
ACE2
ssRNA