Cytokine Storm Syndrome in SARS-CoV-2

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Cytokine storm syndrome is a cascade of escalated immune responses disposing the immune system to exhaustion, which might ultimately result in organ failure and fatal respiratory distress. Infection with severe acute respiratory syndrome-coronavirus-2 can result in uncontrolled production of cytokines and eventually the development of cytokine storm syndrome. Mast cells may react to viruses in collaboration with other cells and lung autopsy findings from patients that died from the coronavirus disease that emerged in 2019 (COVID-19) showed accumulation of mast cells in the lungs that was thought to be the cause of pulmonary edema, inflammation, and thrombosis.

COVID-19 SARS-CoV-2 mast cells cytokine storm vaccine

1. Cytokine Storm Syndrome Occurs during Viral Infection and Inflammation

During an immune response, the cytokine storm phenomenon arises when homeostasis is not returned, and the pro-inflammatory pathways are without regulation and are hyperactive [1][2][3]. Rather than being thought of as a specific disease, the cytokine storm syndrome is considered to be a culminating endpoint to numerous diseases and conditions that occur during an attempt to fight off infections [1][4].

Cytokine storm syndrome was initially observed after systemic infections which took on a similar appearance to that of influenza infections. However, it was difficult to identify since it is not directly associated with any one pathogen or insult to a host, but is rather a common product of the host's immune system responding to any number of pathogens or insults [1]. There are some commonly observed signs and symptoms in cytokine storm syndrome such as fever, systemic inflammation, multi-organ failure, and high concentrations of circulating cytokines [1][5]. It is crucial to determine the underlying cause of the cytokine storm as it will impact the prognosis, symptoms, and treatments that should be administered [1][2]. An important and difficult distinction that is required to properly treat cytokine storm syndrome is differentiating between the concentrations of cytokines and the magnitude of immune responses needed for fighting off the underlying cause of the cytokine storm, and those that are unnecessary and will ultimately cause harm [1].

Cytokines, including interferons (IFNs), interleukin (IL)-6 and IL-1, are observed to be amplified during immune responses against viruses; all of which are associated with the cytokine storm [2][5]. Multiple viruses, including different subtypes of influenza A virus, have been observed to cause infections that can result in cytokine storm syndrome [3]. The gravity of viral infections is in part due to the degree of virulence as well as the nature of the

immune response, which creates an ideal circumstance for the development of cytokine storm syndrome [5]. Although there are general anti-viral responses generated by the body, the overall response produced in the host will differ for each viral infection depending on several factors including the virus's method of infection, mechanism of action, localization, and viral replication rate; all of which will influence the overall cytokine profiles that will be produced in the host during the immune response, as well as the likelihood of a cytokine storm syndrome developing [2][5].

Treatment for a viral infection that consequently triggers cytokine storm syndrome would be to treat both the infection—with anti-viral medications—and the inflammatory syndrome with anti-inflammatory drugs. A challenge with treating a viral infection that is causing a cytokine storm syndrome is differentiating the dysregulated inflammatory responses from the protective ones [6]. The cytokine profiles induced in the host by the underlying viral infection can assist in determining the most appropriate anti-inflammatory drugs or other therapeutic agents to be administered [3]

2. Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV)-2 May Result in Cytokine Storm Syndrome

Cytokine storm syndrome is a cascade of escalated immune responses that can cause the immune system to become exhausted, which might ultimately result in organ failure and fatal respiratory distress [7]. In the context of infections with SARS-CoV-2 that can cause the coronavirus disease that emerged in 2019 (COVID-19) in some people, cytokine storm syndrome is likely the only feature that contributes to severe cases of the disease [8]. When SARS-CoV-2 infects the body, inflammatory responses play a vital role in the response to the virus. However, unregulated innate and adaptive immune responses of the host caused by SARS-CoV-2 result in uncontrolled production of cytokines and eventually can result in the development of cytokine storm syndrome [9].

Cytokine storm syndrome can lead to apoptosis of epithelial and endothelial cells in the lungs, vascular leakage, and acute respiratory distress syndrome (ARDS) [6]. It is believed that ARDS has been responsible for a substantial number of deaths among patients diagnosed with severe COVID-19. Therefore, ARDS can be considered a characteristic immune-mediated clinical feature of SARS-CoV-2 infections. This is consistent with the existing evidence on the original SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, the other well-known coronavirus infections with considerable resemblance to COVID-19 [10]. Although SARS-CoV-2 has shown phylogenetic similarities to both SARS-CoV and MERS-CoV, it seems more likely to result in a cytokine storm compared to the other two [11].

3. Mast Cell (MC) Responses to SARS-CoV-2 May Promote Cytokine Storms

MCs are granulated leukocytes [12] that reside in mucosal interfaces in close contact with the environment to respond to environmental challenges [13] and infectious organisms [14][15][16]. Recent studies showed that MCs are

key effector cells of the innate immune system, and during viral infections they release several inflammatory mediators and cytokines, including histamine and IL-6 [17][18]. Histamine can contribute to the progression of inflammatory responses in many cell types and local tissues by enhancing the secretion of pro-inflammatory cytokines, such as IL-1α, IL-1β, IL-6, and chemokine (C-C motif) ligand 3 (CCL3) [19]. Production of IL-6 might be detrimental during viral infections, promoting virus survival and/or exacerbation of clinical disease [20]. This could be due to polarization of helper T cells into a T helper-2 phenotype (impairing IFNγ production), failure in cytolytic activity, or promoting infected cell survival by inhibiting apoptosis. Knowing that MCs detect multiple classes of viruses, including both DNA and RNA viruses, one may consider MC responses to viruses an enhanced inflammation that has the potential to be harmful [19].

Coronaviruses have now become one of the main respiratory pathogens that cause extreme inflammatory outbreaks of acute pneumonia in individuals [21]. Evidence has shown a potential association of MCs with COVID-19, and the activation of MCs located in the submucosa of the respiratory tract by SARS-CoV-2 is known to lead to the release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. Moreover, autopsy findings from the lungs of patients that died from COVID-19 showed accumulation of MCs that was speculated to be the cause of pulmonary edema, inflammation, and thrombosis in COVID-19 pathophysiology [16][22][23].

The primary receptor that the SARS-CoV-2 spike (S) protein uses to facilitate viral entry into cells has been identified as angiotensin-converting enzyme (ACE)-2 [24]. The ACE2 protects against lung injury, and its downregulation is associated with serious lung injuries. Increasing ACE2 concentrations can correct for arterial hypoxia and improve pulmonary circulatory haemodynamics [25]. Interestingly, ACE2 serine protease in MCs is known to transform angiotensin I to angiotensin II [26] and is required for SARS-CoV-2 binding and entry into target cells. Glycoprotein spikes on the virus's outer envelope bind to the extracellular domain of the ACE2 receptor and allow the virus to enter the target cell [27]. MCs can give rise to bronchoconstriction, both by initiating a renin-angiotensin-generating system in the lungs and by producing leukotrienes [28]. Transmembrane serine protease 2 (TMPRSS2), which can be produced by MCs, is necessary for the priming of the coronavirus spike protein [16], and MC-derived serine protease tryptase, has been observed to be essential for SARS-CoV-2 infection [29][30]. Inhibition of viral entry into the lung cells by serine protease inhibitors such as camostat mesylate has confirmed these findings [31].

Besides pro-inflammatory cytokines and chemokines, MCs are also known to secrete chymase [32], a type of serine protease. Chymase activates transforming growth factor beta (TGF-β), and matrix metalloproteinases [MMP] such as MMP-9 [33] which are involved in pulmonary fibrosis. Moreover, thromboxanes and platelet-activating factor (PAF) produced by MCs can lead to microthrombosis in the lungs and cause COVID-19-associated coagulopathy, which has been confirmed in postmortem analysis of patients who died due to COVID-19 [22].

A study done by Afrin et al. indicated a similarity between the prevalence of MC activation syndrome (MCAS) and that of severe cases of COVID-19. Many aspects of hyper inflammation in patients with COVID-19 seem to be coordinated with MCAS, while drugs which are unlikely to show potency against viral diseases seem to be effective against both MCAS and SARS-CoV-2-induced hyperinflammation [34]. COVID-19 is now widely recognized to be

linked to a variety of extra-pulmonary symptoms, such as multisystem inflammatory syndrome (MIS-A). Symptoms of MIS-A and how stress exacerbates them are somewhat similar to those of MCAS [16].

4. MC Activators May Enhance COVID-19 Vaccine-Induced Immunity

Often overshadowed by their involvement in pathology, MCs play an important role in protective immunity as multi-equipped pathogen sensors. MCs express a variety of receptors such as Toll-like receptors (TLRs), FcεRI-III/IgE, and cytosolic sensors that allow them to detect a wide range of pathogens such as bacteria and viruses, as well as toxins and allergens [12]. In the detection of viruses, MCs rely on the expression of TLR2, TLR3, TLR7, TLR8, TLR9, melanoma differentiation-associated protein 5 (MDA5), and retinoic acid-inducible gene (RIG)-I [12]. Activation through these sensors leads to the *de novo* synthesis of cytokines and chemokines for the generation of a virus-focused response as opposed to degranulation mediated through IgE-induced activation [12][35]. In response to viral infection, MCs not only aid in the innate immune response through recruitment of natural killer cells via production of IL-8, but also influence the adaptive response in numerous ways [36]. For example, MC production of TNF-α recruits dendritic cells (DCs) to the site of infection, which then traffic to draining lymph nodes where antigen presentation takes place [37][38]. Interestingly, MCs are able to induce $CD8^+$ T cell responses through the modulation of DC phenotype as well as recruit T cells to sites of infection through the production of CCL5 [39]. Due to the ability of MCs to detect a wide array of pathogens and modulate naturally acquired adaptive immunity, many efforts are focused on the identification and characterization of MC activators that may be useful as adjuvants to enhance vaccine-induced immunity.

In roughly a year since the COVID-19 pandemic began, a handful of vaccines with evidence of protective efficacy, such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have been developed and are currently being administered in numerous countries around the world [40][41]. The majority of the COVID-19 vaccines that have been developed target the SARS-CoV-2 S protein with the goal of generating neutralizing Abs capable of binding to SARS-CoV-2 virions to prevent infection [42]. Unfortunately, numerous SARS-CoV-2 variants with mutations in the S protein have appeared and exhibit reduced sensitivity to certain antibodies that could neutralize earlier forms of the virus [43][44][45][46]. Furthermore, many COVID-19 vaccines appear to be less effective against certain SARS-CoV-2 variants. For example, the AstraZeneca COVID-19 vaccine was found to have only 10.4% efficacy against the B.1.351 (501Y.V2) variant that was first identified in South Africa [47]. To further compound issues, slow vaccination programs have introduced a narrow selection pressure against the S protein into the population, which may further promote the emergence of a full SARS-CoV-2 vaccine escape mutant [48][49]. These concerns emphasize the need for second-generation COVID-19 vaccines capable of generating a broader immune response that is not only focused on inducing SARS-CoV-2 S protein-neutralizing antibodies. Second-generation vaccines must also prioritize robust anti-SARS-CoV-2 cellular-mediated immunity through the targeting of additional SARS-CoV-2 proteins rich in T cell epitopes, such as the SARS-CoV-2 nucleocapsid protein [50]. Interestingly, recent studies of individuals who recovered from natural infections suggest that T cell-mediated immunity plays a larger role in protection against SARS-CoV-2 than previously thought [51][52]. Especially important is the T helper cell response

induced upon infection. Interestingly, compared with severe cases, people who recovered from mild COVID-19 also had more robust memory $CD8^+$ T cell responses in the respiratory tract [50]. Furthermore, long-term immunity and control of re-infection appears to be largely antibody-independent but T cell-dependent [53]. Considering the ability of MCs to respond to viral infections and enhance T cell responses, we promote the investigation of mast cell activators as adjuvants for COVID-19 vaccines with the goal of enhancing the magnitude and longevity of SARS-CoV-2-specific T cell responses.

Here, we summarize two MC activators capable of enhancing anti-viral adaptive immunity that are worthy of further investigation as potential adjuvants in COVID-19 vaccines. A focus is placed on antibody- and cell-mediated responses and the overall T helper cell response.

4.1. Compound 48/80

Compound 48/80 (c48/80) is a widely studied MC activator and is a potent mucosal adjuvant [35]. It is a synthetic polymer that stimulates the degranulation of MCs in an IgE-independent manner to evoke an inflammatory response [54]. Following activation with c48/80, MCs produce TNF-α which promotes DC and T cell functions. leading to significant trafficking of DCs to draining lymph nodes (DLNs) [37]. Numerous studies have demonstrated the ability of c48/80 to induce high concentrations of serum IgG and mucosal soluble IgA when co-administered intranasally with viral glycoproteins [55][56][57]. Additionally, c48/80-adjuvanted responses were shown to enhance protection in challenge models using lethal doses of H1N1 influenza virus, as well as vaccinia virus [56][57]. Interestingly, a follow up study on influenza demonstrated the inability of c48/80 to enhance protection against H1N5 challenge, suggesting that the adjuvanticity of c48/80 may vary depending on the immunogen utilized [58]. Similarly, the T helper cell responses induced by c48/80 also varied between studies [55][57]. One study co-administering c48/80 with the hepatitis B virus glycoprotein found a T helper-2-biased response while the studies focusing on the H1N1 influenza found a balanced T helper-1/T helper-2 response [55][57]. However, it is important to note that the study immunizing with hepatitis B virus glycoprotein utilized a chitosan nanoparticle platform, which may be related to the T helper-2 bias [55]. While the T helper cell response was not characterized in the study utilizing vaccinia virus, c48/80 induced only a modest increase in the number of $CD8^+$ T cells, potentially indicating a T helper-2 bias [56]. In contrast with these studies, one group investigated the ability of c48/80 to enhance $CD8^+$ T cell-mediated protective immunity utilizing the nucleoprotein of the H1N1 influenza virus [59]. This group found that c48/80 induced high levels of IgG1 and IgG2a in similar proportions, indicating a potentially well balanced T helper-1/T helper-2 response [59]. More importantly, it induced a higher number of nucleoprotein-specific $CD8^+$ T cells compared to $CD4^+$ T cells. The c48/80+nucleoprotein combination provided 100% protection in mice when challenged with homologous H1N1 influenza virus and even protected against heterologous challenge using the H9N2 strain of influenza virus [59]. While high concentrations of serum IgG and secretory IgA were produced in these mice, the fact that the nucleoprotein is contained within virus particles and infected cells suggests that the nucleoprotein-specific $CD8^+$ T cells were the main correlate of protection against virus challenge [59]. Based on these studies, c48/80 appears to be a potent mucosal adjuvant capable of inducing protective antibody- and cell-mediated immunity against certain viruses. While potentially promising for use as an adjuvant in COVID-19

vaccines, the immunogen-dependent effect of c48/80 and variability in T helper cell responses necessitates extensive investigation.

4.2. Interleukin-18

When investigating the adjuvant ability of the IL-1 family of cytokines in combination with a recombinant influenza virus hemagglutinin protein via intranasal vaccination, Kayamuro et al. found that only four cytokines, IL-1α, IL-1β, IL-18, and IL-33 correlated with high concentrations of serum IgG and secretory IgA [60]. Upon further analysis, they discovered that the adjuvancy of IL-18 occurred in a MC-dependent manner and led to the recruitment of DCs and T cells to the site of immunization [60]. Upon re-stimulation of splenocytes *in vitro*, mice treated with IL-18 as an adjuvant had increased concentrations of both T helper-1- and T helper-2-associated cytokines (IFN-y, IL-4, and IL-5), and enhanced numbers of $CD8^+$ T cells. In an influenza challenge model, IL-18 significantly enhanced protection (100% survival). Additionally, adjuvanting with IL-18 resulted in induction of a balanced ratio of IgG1/IgG2a. As such, IL-18 may be a useful adjuvant for COVID-19 vaccines.

Conclusions

In some people, SARS-CoV-2 can cause the uncontrolled production of cytokines and the development of cytokine storm syndrome. Evidence indicates that MCs can respond to SARS-CoV-2 and accumulate in the lungs of patients with COVID-19, where they correlate with pulmonary edema, inflammation, and thrombosis. MCs are foundational drivers of inflammation [61] that produce preformed inflammatory mediators and cytokines upon activation. Preventing the release of mast cell-derived mediators and impeding the impacts imposed by these mediators could blunt the severity of COVID-19. Additionally, MC activators could be considered for testing as adjuvants for COVID-19 vaccines. Further, the medications that target the performance of MCs could be potentially of value in the treatment of COVID-19. The recognition of the cytokine storm initiated by MCs is crucial for the proper treatment of COVID-19 in patients and could potentially lead to novel clinical approaches for many pathological conditions in which cytokine storm or cytokine release syndromes are life-threatening features.

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