Immunopathogenesis of COVID-19

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The coronavirus disease 2019 (COVID-19) is caused by the infection of the novel highly contagious severe acute respiratory syndrome virus (SARS-CoV-2), viral infection can cause acute respiratory distress syndrome (ARDS) and, in severe cases, can even be lethal. Behind the inflammatory process lies the so-called cytokine storm (CS), which activates various inflammatory cytokines that damage numerous organ tissues.

OVID-19 cytokine storm

1. Introduction

As of 2023, the coronavirus disease 2019 (COVID-19) pandemic has been successfully contained in most parts of the world thanks to effective vaccination, a high proportion of people having successfully fought it off (with or without vaccination), public health strategies, and effective novel treatment methods. It no longer poses such an immediate global public health and socio-economic threat as it used to, mainly in 2020 and 2021. As the WHO Director-General Tedros Adhanom Ghebreyesus said in March 2023 “I am confident that this year we will be able to say that COVID-19 is over as a public health emergency of international concern” [1]. However, these optimistic future perspectives should be interpreted with caution, because the evolutionary trajectory of SARS-CoV-2 is uncertain. Future local outbreaks and new variants will likely have to be dealt with [2]. Even if future infections are mild from the epidemiological perspective and reserved for local epidemics, COVID-19 will not cease to be a dangerous disease with many potentially life-threatening complications resulting from the dysregulated release of proinflammatory cytokines, known as the cytokine storm (CS) [3]. These are only some of the scenarios to consider and prepare for to diminish the debilitating effect of a future pandemic [4]. Pointing toward possible future complications are issues such as the emergence of new variants and the global disparities in vaccine distribution and access. Recently, Wang et al. reported alarming antibody evasion properties in Omicron subvariants BQ and XBB, which, due to the mild clinical presentation of Omicron infection, do not pose an urgent problem; however, this tendency to evade antibodies could significantly hinder vaccination strategies [5].

Moreover, there is still the relevant issue of long-COVID, which remains a persistent problem for many patients around the globe, with the cumulative prevalence ranging between 9 and 63% [6]. Therefore, the development of state-of-the-art therapeutic approaches combating COVID-19 concerning CS-related complications is still a timely area of research, which can provide better outcomes for COVID-19 patients but also can serve as a foundation for the development of therapeutic strategies for potential pandemics that could strike in the future. Many approaches have been implemented to combat CS-induced COVID-19-associated complications, e.g., corticosteroids, hydroxychloroquine, chloroquine, or tocilizumab [7]. There are also strategies that attempt to implement knowledge

regarding the immunoregulatory effect of mesenchymal stem cells (MSCs) and their derivatives (conditioned media (CMs), or more specifically, exosomes forming the base of cell-free therapies). Among different cell populations, MSCs undoubtedly possess numerous benefits as a cell-based treatment for COVID-19 patients, as evidenced by several already-finished and countless ongoing clinical studies [8]. According to the specific abilities of MSCs, such as the regulation of innate and adaptive immune response, they are indisputable candidates not only for COVID-19 but also for other immune-mediated inflammatory diseases. However, MSCs may present limitations in delivery, safety, proper engraftment, differentiation, and overall therapeutic efficacy.

On the other hand, MSC derivatives, such as CMs or extracellular vesicles (EVs), are more clinically suitable thanks to their fundamental properties in immunomodulation and wound healing [9][10]. Moreover, according to extensive research, it is now widely accepted that MSCs are therapeutically effective mainly due to their paracrine secretion that mediates cell-to-cell signaling. On account of this, it was proved by several studies that MSC derivatives possess therapeutic effects similar to MSCs themselves, involving anti-inflammatory, regenerative, proangiogenic, and anti-protease qualities [11][12]. Regarding the transport of MSCs and their derivatives, MSCs are usually transferred to the body intravenously. On the contrary, thanks to the small size of EVs, there might be an alternative route of administration, such as inhalation, enabling direct pulmonary delivery [13]. Therefore, MSC derivatives can be more convenient and safer, with more significant potential for clinical translation. Other benefits of MSC derivatives include eliminating host immune reactions; the possibility of long-term storage without harmful content in cryopreservation media and without significant loss in bioactivity; and overall cost-effectivity, enabling their mass production [14].

2. Immunopathogenesis of COVID-19

Immunopathogenesis is generally defined as a mode of disease development with a substantial contribution of innate and adaptive immune system mechanisms, which, upon dysregulation, cause collateral damage, promoting further disease development and its complications [15]. In 2005, Dandekar and Perlman published a paper on SARS-CoV, a virus responsible for SARS infection wreaking havoc between 2002 and 2004. The authors reported that a dysregulated immune response is essential to its pathogenesis, which can lead to life-threatening complications. Ironically, the authors concluded that “lessons from such studies will help us to understand more about the pathogenesis of SARS in humans and to prevent or control outbreaks of SARS in the future” [16]. Less than two decades later, a new SARS-CoV-2 strain struck the world, bringing severe socio-economic and public health challenges. Not only had this new outbreak failed to be prevented, but it was also more severe by several orders of magnitude than the original SARS-CoV virus. Fortunately, many insights, research endeavors, and experiences from fighting the original virus helped us understand the foe better. From the immunopathogenic perspective, the most dreaded complication during COVID-19 is immune system dysregulation, known as CS. Alternatively, it can be referred to as cytokine release syndrome or cytokine-associated toxicity. It is characterized by hyperinflammation, which is damaging to the surrounding tissues. Its hallmark is excessive cytokine release which fails to contain the immune system response to the harmful pathogen elimination and orchestrate the resolution of inflammatory responses to the previous baseline state [17]. In the case of inadequate treatment, it can

lead to multiorgan dysfunction or even multiorgan failure with possibly fatal consequences [18]. Initially, COVID-19 was considered a respiratory condition, primarily affecting the lungs and causing viral pneumonia. Soon after, a thorough investigation of the SARS-CoV-2 and COVID-19 pathogenesis revealed that altered immune system regulation is integral to COVID-19 multiorgan involvement and severe extrapulmonary complications. The first indication that COVID-19 should be considered from the immunopathogenic standpoint was a change in patients' leucogram, which showed lymphopenia and an enhanced neutrophil–lymphocyte ratio [19][20]. Fighting off the SARS-CoV-2 virions and subsequent COVID-19 development is heavily influenced by the components of the innate and adaptive immune systems alike.

Innate immune responses are mediated through the interaction between viral pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs), e.g., Toll-like receptors (TLRs) on the surface of host innate immune cells, such as neutrophilic granulocytes, macrophages, and NK cells, leading to the secretion of proinflammatory cytokines. The adaptive immune response is mediated by the recruitment of CD8+ cytotoxic T-lymphocytes (CTLs), CD4+ helper T-lymphocytes (Th cells), and antibodies-producing B-lymphocytes [21], although B-lymphocytes usually do not contribute to the CS [18]. CD4+ helper T-lymphocytes are differentiated into subclasses, namely Th1, Th2, Th9, and Th17. Th1 and CTLs are routinely identified as cells fighting off viral infections, whereas the excessive Th1 response is most often associated with CSs [18]. Especially significant is the population of CD4+ PoxP3+ regulatory T-lymphocytes (Tregs), whose primary role is the attenuation of immune responses and keeping them adequately reserved to the noxious stimuli without overactivation, which is deleterious to the host tissues. They can be thought of as cells responsible for immune homeostasis. In the case of COVID-19, the proper function of Tregs protects from hyperinflammation and CS-induced tissue damage. Therefore, Treg targeting has been used as a promising therapeutic approach [22]. A delicate balance of all these cell populations is essential for the immune reaction to kill off the invading pathogens with minor damage to healthy surrounding tissues. Unfortunately, the exact opposite occurs during COVID-19.

An important immunopathogenic factor in COVID-19 is immune cell exhaustion, broadly defined as immune cell fatigue resulting from a robust initial immune response [23]. Xang et al. reported that CS might promote T-lymphocyte exhaustion [24]. This combination of immune cell dysfunction and hyperinflammatory CS leads to a poor COVID-19 prognosis. The panel of cytokines responsible for the CS is vast. As reviewed by Montazersaheb et al., cytokines involved in the COVID-19 immunopathogenesis include the Interleukin (IL)-1 family, IL-6, IL-10, IL-17, interferon-gamma (INF γ)-inducible protein 10 (IP-10), and tumor necrosis factor-alpha (TNF-α) (a more proper official term, TNF, will be used from now on [25]), among many others [26].

The IL-1 family of cytokines comprises IL-1, IL-18, IL-33, IL-36, IL-37, and IL-38. Collectively, these proinflammatory cytokines activate NLRP3 inflammasomes [27], leading to cell death VIA pyroptosis [28]. On the one hand, this type of cell death has been associated with host resistance to pathogen invasion. However, on the other hand, pyroptosis can bring about overwhelming hyperinflammation [29].

IL-6 is the cardinal cytokine implicated in the immunopathogenesis of CS, also serving as a predictor of COVID-19 clinical outcomes and mortality [30]. In 2020, Coomes and Haghbayan published a systematic review and meta-

analysis which revealed that COVID-19 patients with a complicated course of the disease have a 2.9-fold increase in serum IL-6 concentration compared to those with mild symptoms and good outcomes. IL-6 levels correlated with adverse clinical outcomes such as ICU admission, ARDS development, or death [31]. Considering the crucial role of IL-6 in COVID-19 prognosis, many studies have targeted IL-6 pathways as a potential therapeutic approach. One of the many drugs tested for COVID-19 management is tocilizumab—an IL-6 receptor (IL-6R) inhibitor. Galván-Román et al. retrospectively studied COVID-19 inpatients and found that IL-6 levels above 30 pg/mL best predicted the need for invasive mechanical ventilation. The administration of tocilizumab improved oxygenation and decreased mortality [32].

IL-10 is another cytokine which is significantly elevated during COVID-19 and correlates with poor clinical outcomes. Although generally functioning as an anti-inflammatory cytokine, its high levels in severe COVID-19 may seem counterintuitive at first glance. There are several hypotheses on the possible mechanisms behind its action. Islam et al. reported that IL-10 fails to suppress the hyperinflammatory state, or its anti-inflammatory activity is not universal [33]. The pleiotropic activity of IL-10 was also discussed by Lu et al., who hypothesized that IL-10 could act as a proinflammatory cytokine under certain conditions [34]. An alternative explanation has similar features as the first one. It is the state of “IL-10 resistance”, defined as the inability of immune cells to respond to IL-10-mediated immune suppression appropriately. This explanation is corroborated by the observations of severe COVID-19 in patients with type II diabetes, who were previously shown to have diminished IL-10 action due to hyperglycemia [33][35]. The meta-analysis and regression published by Dhar et al. showed that out of the many cytokines elevated in COVID-19, IL-10 and IL-6 alone are sufficient to determine and predict the risk of the severe clinical course of the disease, allowing for early interventions which will result in better prognoses [36]. The important role of IL-6 and IL-10 is rooted in their ability to regulate antibody production by influencing the differentiation and maturation of B-lymphocytes [37]. Heine et al. conducted a clinical trial where they found that autocrine IL-10 secretion by B-lymphocytes themselves induced their differentiation into IgM- or IgG-secreting plasmablasts [38]. The effective production of protective antibodies is generally associated with a good COVID-19 outcome; however, there have been reports on harmful autoantibodies whose production can be life-threatening. Bastard et al. found that severe COVID-19 patients can produce IgG antibodies against type I interferons (IFNs) which normally help block SARS-CoV-2 infection [39]. The detrimental role of IL-6 and IL-10 was previously reported in various autoimmune disorders [40][41].

Type III IFNs are anti-viral cytokines comprising four IFN-λs which are vital for the normal regulation of anti-viral response in the respiratory system. Their central role is to limit the infection by the means of viral resistance induction. IFN-λs are anti-inflammatory and responsible for tissue protection. In the context of COVID-19, IFN-λs can be regarded as CS preventers [42]. Moreover, Broadbent et al. found that the endogenously activated IFN-λ1 pathway provides resistance against SARS-CoV-2 infection [43].

IL-17 (IL-17A) is the proinflammatory cytokine produced by Th17 cells. Of the many cytokines produced upon infection with SARS-CoV-2, IL-17 is most often associated with pulmonary inflammation. Along with IL-6 and IL-8, IL-17 seems to be a principal cause of pulmonary fibrosis. IL-17 is also a potent activator of other proinflammatory cytokines released from various lung alveoli cells, including epithelial cells, endothelial cells, and alveolar

macrophages [44]. Maione et al. summarized that IL-17 could be associated with COVID-19 severity and progression. They described it as a “rheostat” of the COVID-19 immune response [45].

IP-10 is a chemokine synthesized by various cells as a response to INFγ. IP-10 regulates CD4+ and CD8+ T cells, natural killer cells, and dendritic cells. Bunprakob et al. studied plasma samples of patients with various disease severity and concluded that IP-10 elevation is directly proportional to disease severity [46]. Chen et al. also reported that serum IP-10 could be a biomarker of COVID-19 severity and is associated with mortality risk [47]. Similar results were published by Mulla et al., who evaluated a panel of four cytokines, including IP-10, and found that its serum levels are significantly higher in critically ill patients [48].

TNF is a pleiotropic cytokine involved in regulating acute and chronic inflammation. It can mediate apoptosis, cell proliferation, and the release of other cytokines. Physiologically, it controls tumor formation and immune system homeostasis. Its dysregulation can lead to CS in COVID-19 patients [49]. Jia et al. reported serum TNF as an independent risk factor for death in patients with a severe course of the disease [50]. Some authors view TNF as the central mediator of CS, implicating it in blood clotting activation, lung damage, or even heart failure. Thus, the therapeutic targeting of NF-κB-mediated TNF signaling might significantly decrease mortality rates [51].

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