IMMUNOREGULATION

Winter & Spring 2023. Volume 5. Number 2

Review Paper
Type I Interferon and COVID-19: Disease Severity

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Citation Rahimlou B, Ghazanfari MR, Ghambari Mohammadi N. Type I Interferon and COVID-19: Disease Severity. Immunoregulation. 2023; 5(2):73-90. http://dx.doi.org/10.32598/Immunoregulation.5.2.8

http://dx.doi.org/10.32598/Immunoregulation.5.2.8

Article info:
Received: 06 Jun 2022
Accepted: 25 Dec 2022
Available Online: 01 Jan 2023

Keywords:
Plasmacytoid dendritic cell, Type I interferon, COVID-19, SARS-CoV-2, Antiviral response, Risk factor, IFN signature

ABSTRACT

Upon viral infection, the release of type I interferons (IFNs) plays a crucial role in limiting viral replication, reducing tissue damage, and boosting both innate and adaptive immune responses. A plasmacytoid dendritic cell (pDC) is a professional type I IFN-producing cell with the ability to produce large amounts of type I IFN quickly. However, when pDCs experience dysfunction or impairment in their ability to produce type I IFNs, the susceptibility to severe viral infections increases. Patients with severe COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), exhibit lower levels of pDCs and diminished type I IFN responses compared to individuals with mild or asymptomatic disease. This association between severe COVID-19 and compromised IFN responses extends beyond underlying chronic illnesses. This review will also discuss the dysregulation of the pDC/type I IFN axis in COVID-19 and highlight the critical role of type I IFN-dependent factors contributing to the severity of COVID-19. Additionally, the impact of the IFN signature on a patient's immune response to SARS-CoV-2 infection will be investigated.

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1. Introduction

There was a worldwide outbreak of coronavirus disease 2019 (COVID-19) in 2019 caused by a single-stranded RNA virus known as SARS-CoV-2 (SARS-CoV-2) [1]. More contagious viral virus strains have developed since the pandemic's start, causing fresh waves of the disease [2]. The course and outcome of COVID-19 are strongly influenced by an individual's immunological condition, which may range from no symptoms to moderate to severe symptoms [3]. Clinical manifestations and recommended treatment can generally be divided into three distinct stages for COVID-19 [4]. After an infection, there is an incubation period known as the early phase of an infection. In this stage, there are usually no symptoms or they are accompanied by minor, nonspecific symptoms, like malaise, fever, and dry cough. COVID-19 is typically limited to this stage and the prognosis is generally very good. Already, the second stage has been linked to pulmonary involvement, whether or not hypoxia was present. COVID-19 patients typically cough, have fevers, or experience hypoxia. They need hospitalization at this point to be closely monitored or treated. A cytokine storm is defined as a third-stage inflammation that causes extrapulmonary, systemic inflammation, leading to lymphopenia and the loss of T cells that help, regulate, and remember [5]. An increase in neutrophil count and inflammatory cytokines and biomarkers has been observed [6]. A cytokine profile resembling secondary haemophagocytic lymphohistiocytosis—characterized by elevated levels of IL-2, IL-7, IFN-γ inducible protein 10 (IP-10), granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1 (MIP-1α), monocyte chemoattractant protein 1 (MCP-1), and tumor necrosis factor-α (TNF-α) may be seen in patients with this advanced stage [7]. Acute respiratory distress syndrome, cardiopulmonary collapse, myocarditis, systemic organ involvement, septic shock, and even vasoplegia may also develop at this stage [4]. The prognosis for this stage of the illness can be quite bad for individuals who do not recover from the critical stage. In addition to the disease's well-known respiratory pathology, COVID-19 has been found to cause a variety of other extrapulmonary manifestations. Among them are the skin, genitourinary, gastrointestinal, and central nervous systems [8]. Acute coronary syndrome, acute kidney injury, thrombotic complications, myocardial dysfunction, arrhythmias, gastrointestinal symptoms, hepatocellular injury, hyperglycemia, ketosis, dermatologic complications, preeclampsia, and fertility issues are symptoms that can indicate multiple organ involvement [9]. Aside from COVID-19 syndrome, survivors may also suffer from post-COVID-19 syndrome, which adversely affects their quality of life for months afterward. There are a variety of clinical symptoms associated with the post-COVID-19 syndrome, including pulmonary embolism, deep vein thrombosis, acute myocardial infarction, depression, anxiety, myalgia, dyspnea, fatigue, impaired memory, and concentration, as well as a variety of neuropsychiatric syndromes [10].

As a general rule, post-COVID-19 syndrome occurs in 10–35% of individuals, but it can rise as high as 85% among hospitalized cases with SARS-CoV-2 infections [10]. The COVID-19 severity and fatality are more likely to occur in chronically ill patients with ailments, such as diabetes, hypertension, and cardiovascular disorders [11]. As research continues to emerge on COVID-19, it appears that patients with abnormal interferon (IFN) antiviral responses are much more likely to experience severe symptoms. So far, obese patients are more likely to die than older people, men, pregnant women, or pregnant women with normal IFN responses [12]. In response to viruses, interferons, which are the main components of anti-viral defense, inhibit virus replication in healthy people. While, viruses may affect people with genetic disorders of IFN signaling or with autoantibodies produced against type I IFNs that block direct inhibitory effect of type I IFNs on viral replication [13]. The findings demonstrate a notable association between the variability of COVID-19 outcomes and the production of type I interferons (IFNs), indicating that conditions characterized by reduced type I IFN production are linked to unfavorable outcomes. Plasmacytoid dendritic cells (pDCs) serve as the principal producers of type I IFNs in response to viral infections due to their specialized training in identifying viral nucleic acids [14]. Numerous outstanding articles on COVID-19 discuss pDCs and IFNs that are derived from pDCs in the antiviral immune response against SARS-CoV-2 [15]. The function of IFNs and pDCs in COVID-19 has been summarized succinctly in light of the most recent information available in this field. In order to emphasize that individuals with low type I IFN signatures are more likely to have a severe disease outcome due to a variety of inborn or acquired disorders, we presented a detailed overview of the risk factors for COVID-19 severity associated with impaired type I IFN responses and lower number of pDCs.

The role of antiviral IFNs in COVID-19

SARS-CoV-2 is a positive-stranded RNA virus that highly spreads through the respiratory systems. Through the transmembrane serine protease 2 (TMPRSS2) and

the angiotensin-converting enzyme 2 (ACE-2) receptor, the virus enters the nasal mucosa, targeting the most receptive epithelial cells of the nasal mucosa [16]. A possible route of virus transmission has been identified through the alimentary system because SARS-CoV-2 receptors are widely expressed in the gastrointestinal tract [17]. As a consequence of viral infection and active viral replication, cytosolic viral sensors in the respiratory epithelium induce immunological responses in epithelial cells, primarily type III IFNs, and less commonly type I IFNs [18]. There are several ways, in which type III IFNs differ from type I IFNs. Type I IFNs are produced by all nucleated cell types and their receptor is widely expressed. Epithelial cells are the primary producer of type III IFNs, while macrophages, monocytes, and dendritic cells also produce them. Epithelial cells and some immune cells, like monocyte-derived DCs, macrophages, neutrophils, and B cells, express heterodimeric IFN receptors that promote more cell type-specific immune responses, including pDCs, monocyte-derived DCs, monocytes, macrophages, and neutrophils. A type III IFN signaling mechanism is similar to that used by type I IFNs [19]. However, the antiviral effects of these cytokines are different. In contrast to interferon-stimulated gene (*ISG*) production induced by type I IFN, type III IFN-mediated expression of *ISG*s is long-lasting, but low in intensity. Moreover, type III IFNs inhibit viral transmission and dissemination primarily at mucosal surfaces and are less inflammatory than type I IFNs [20]. According to recent research, SARS-CoV-2 can easily pass through the airway epithelium as the first line of defense of the immune system. Because the virus's highly efficient immune evasion mechanisms allow it to induce type I and III IFN responses that are delayed in the nasal epithelium, SARS-CoV-2 produces type I and III IFN responses that comparatively encounter delays with other respiratory viruses [21]. A variety of mechanisms can be employed by SARS-CoV-2 to block IFN signaling, including the inability to obscure pathogen-associated molecular patterns (PAMPs), the interference with IFN synthesis, the inhibition of IFN activity, and the disruption of the signaling cascades [22]. There is also an increase in IFN resistance associated with recently emerged SARS-CoV-2 variants with mutated nonstructural proteins (NSPs) [23]. Dendritic cells and macrophages provide innate immune responses to viruses that manage to penetrate the first line of defense. In contrast to the epithelium, these cells produce the majority of type I IFNs, including IFN-α and IFN-β. In contrast to type III IFNs, type I IFNs are more pleiotropic cytokines. IFNs of type I not only induce antiviral activity but also promote antigen presentation, support NK cell function, and regulate B and T cell responses [24]. In addition to maintaining synaptic plasticity of the central nervous system, managing the function of hematopoietic stem cell niches, bone regeneration, and regulating optimal antiviral responses, type I IFNs also regulate a variety of physiological processes [14]. Keeping the body's baseline IFN production is crucial to maintaining a person's ideal IFN signature, which is a result of the most recent IFN-mediated process [25]. A macrophage or myeloid DC secretes IFN primarily by activating cytosolic retinoic acid-inducible gene (*RIG*)-I-like helicases, while a pDC synthesizes IFN primarily by activating Toll-like receptors (TLRs) that detect viral nucleic acids. Due to their extraordinary ability to produce large amounts of type I IFN, pDCs are often referred to as "professional" type I IFN-producing cells. Upon viral infection, they can produce up to 10 pg/cell [26]. It is at least ten times greater than the production of IFN by monocytes [27]. The type III IFN receptor can be found on pDCs in addition to producing type I IFNs. It is also possible to induce type III IFN production in pDCs by viruses and artificial TLR agonists, like CpG-A; however, this kind of IFNλ1 is produced at levels that are roughly ten times lower than IFNα by pDCs. In response to viral infection, pDCs often produce more IFNα than IFNλ. The IFNacts primarily as an autocrine signal, promoting survival of pDCs by increasing IFNλ production [28].

In a study on mild and severe COVID-19 patients, it was found that type I and III IFNs predominated in patients' upper airways and regulated protective *ISG* expression. Similarly, patients with severe to critical illness may have elevated type I IFN and IFNλ2 expression. Similarly, patients with severe COVID-19 express higher levels of type I IFNs and IFNλ2 in the lower airways, but their expression of type IFNλ1 and IFNλ3 is diminished. There is strong pro-apoptotic expression of p53 in conjunction with poor induction of *ISG* [29]. In order to overcome viral infections, it is essential to control IFN responses. Research on Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) infections, as well as the most recent COVID-19 trial data, indicates that IFN response timing influences disease outcome. When the viral load is still relatively low, early induction of IFN leads to rapid viral clearance and moderate illness. When viral load is high, the immune system is unable to respond to IFN as a result of viral defense mechanisms resulting in a delayed IFN response. The delayed response encourages viral persistence and induces innate immune cells to produce inflammation-inducing cytokines, resulting in tissue damage and excessive inflammation [30]. An analysis of the characteristics of IFN response in COVID-19 pa-

tients was published in a recent paper with an excellent summary table that supports the hypothesis that the severity of COVID-19 is largely based on the individual's IFN signature [31].

The role of pDCs in COVID-19

The previous section discussed the importance of an ideal type I IFN response to COVID-19. In addition to being the primary producer of IFNs, pDCs are crucial in defense against infections caused by SARS-CoV-2 in recent years. ACE-2 and TMPRSS2 receptors are not present in human pDCs, which makes them resistant to SARS-CoV-2 in vitro. SARS-CoV-2 can nonetheless enter the cells through transmembrane neuropilin 1 receptors (NRP1 and BDCA4), which are pDC cell surface markers [32]. It has previously been noted that antibody ligation of BDCA4 decreased pDCs' ability to produce type I IFN [33], and more recently, it has been shown that the virus also reduced the pDCs' type I IFN responses when it binds to BDCA4 on pDCs, which can serve as an evasion mechanism [34]. In vitro culture of pDCs shows resistance to SARS-CoV-2 infection. When compared to medium conditions, SARS-CoV-2 stimulation enhanced pDC viability and prevented viral replication. SARS-CoV-2 stimulated pDCs to produce type I IFNs that could potentially rise to 80 ng/mL in response. In addition, pDCs mount a powerful type I IFN response by efficiently generating type I IFNs. Similarly, when SARS-CoV-2 infected cells are cocultured with healthy non-infected cells, four subpopulations of pDCs are shown to differentiate [35]. A strong type I IFN response is observed when pDCs are stimulated with SARS-CoV-2 (PD-L1+CD80-), a subgroup that is characterized by strong differentiation into P1-pDCs (PD-L1+CD80-) [32]. A P1 dominant differentiation is also observed in infected cells [36]. A TLR7-dependent signaling pathway appears to be involved in the type I IFN production of activated pDCs upon stimulation by SARS-CoV-2 [32], and both their diversification and cytokine production are mediated by the adapter molecules IRAK4 and UNC93B1 [35]. As a result of TLR7 activation, pDCs are stimulated to initiate antiviral activity via interferogenic synapses in response to SARS-CoV-2 infected cells [37]. As a result of these in vitro experiments, pDCs were found to induce an antiviral state in host cells, stopping viral replication, and promoting innate and adaptive immune cell antiviral activity. This was demonstrated by triggering type I IFN-dependent antiviral responses against SARS-CoV-2 (Figure 1).

COVID-19 patients with severe/critical infection have lower proportions of pDCs in their bronchoalveolar lavage fluid than those with moderate infection, as revealed by single-cell RNA sequencing [38]. Moreover, Sánchez-Cerrillo et al. discovered a decrease in the number of PCs in the blood of critically ill patients and the absence of infiltrating bronchoscopic infiltrates [39]. As a consequence of inflammation, pDCs migrate to the lungs, explaining why the blood pDC population is lower, but pDCs in the lungs are also lower under severe circumstances. Hyper-inflammatory conditions in the lungs compromise the viability of pDCs and their ability to produce type I IFN, resulting in particularly severe infections. In chronic viral infections, pDC exhaustion overwhelms them, causing them to decrease type I IFN secretion and eventually die by apoptosis. This results in increased virus replication and decreased innate immune response [40]. A study found that the pDCs of COVID-19 patients raise less IFN and mTOR signaling. A study also confirmed that the apoptotic gene profile displayed by pDCs of COVID-19 patients is positively linked to the severity and presence of COVID-19 [41]. Inflammatory lung cytokines significantly influence the ability of pDCs to generate type I IFNs [42], and this is negatively influenced by pro-inflammatory mediators, such as prostaglandin E2 (PGE2), IL-1, and IL-10 in COVID-19 patients [42]. Furthermore, COVID-19 depletes IL-3, an essential survival factor that originates primarily from T cells [43]. Bénard et al. found that IL-3 levels were predictive of COVID-19 severity and outcome. Lower levels of IL-3 were associated with increased viral load, mortality, and severity. Non-survivors had lower T cell counts, while COVID-19 patients showed a correlation between T cell counts and pDC levels. Patients with COVID-19 with pulmonary symptoms had significant IL-3 and CXCL12 levels in their bronchoalveolar lavage fluids (BALFs). As a result of the production of IL-3 by T cells, epithelial cells release CXCL12, which then attracts pDCs to the lungs [44] (Figure 2). The results of these investigations indicate that controlling the SARS-CoV-2 infection and stopping the progression of severe illnesses require the right number of pDCs and type I IFNs. All illnesses and disorders that are characterized by decreased IFN production and low pDC frequency are associated with severe or critical COVID-19 [34]. An analysis of the mechanisms that explain the positive correlation between pDC function and the severity of COVID-19, a description of the characteristics of pDCs during COVID-19, and an evaluation of observations related to pDC fate during COVID-19 are presented in this paper.

Risk factors associated with type I IFN in COVID-19

Reduced production of antiviral IFN is related to genetic and congenital factors: *IRF7*, *IRF9*, *TLR3*, and *STAT2* genes are among the genes associated with severe pneumonia caused by influenza viruses, *IFNAR1*, *IFNAR2*, and *STAT2* are associated with adverse events associated with live attenuated virus vaccines, and *TLR3*, *UNC93B1*, *TICAM1*, *TRAF3*, *TBK1*, *IKBKG*, *IRF3*, *IFNAR1*, and *STAT1* are linked to herpes simplex encephalitis. Type I IFN responses are impaired by congenital genetic defects in the *TLR3* and *IRF7* genes [45]. A recent study conducted on an international group of patients revealed that approximately 3.5% of individuals with critical COVID-19 have loss of function mutations at specific genetic locations. Out of the 659 patients with severe COVID-19, 23 individuals were identified to have either autosomal recessive (*IRF7* and *IFNAR1*) or autosomal dominant (*TLR3*, *UNC93B1*, *TICAM1*, *TBK1*, *IRF7*, *IRF3*, *IFNAR1*, and *IFNAR2*) deficiencies. Additionally, ten patients exhibited low levels of IFNα. Interestingly, autosomal recessive mutations have a higher impact compared to autosomal dominant gene defects in terms of their penetrance [46]. Cells lacking *TLR3*, *IRF7*, or *IFNAR1* demonstrate a heightened susceptibility to SARS-CoV-2, and *IRF7*-deficient pDCs are incapable of generating type I IFNs upon viral exposure [46]. Additionally, cells lacking *IFNAR1* fail to exhibit a response when stimulated with type I IFN. The presence of autosomal recessive IRF7 deficiency in two patients (aged 49 and 50 years) and *IFNAR1* mutation in two other patients (aged 26 and 38) were found. Notably, none of the four patients had a history of hospitalization due to a severe viral illness prior to the onset of COVID-19 pneumonia. This emphasizes that these mutations have a greater impact on susceptibility to COVID-19 compared to seasonal influenza viruses [47]. Furthermore, Van Der Made et al. discovered four male patients in their study who possessed loss-of-function variants of *TLR7*. These individuals experienced severe cases of COVID-19 and were distinguished by their compromised production of both type I and type II IFNs [48]. A different study revealed that recessive *TLR7* deficiency accounts for 1% of critical COVID-19 cases in men under 60 years old [49]. Furthermore, the *IFITM3* gene produces a protein called interferon-induced transmembrane protein 3, which plays a crucial role in limiting viral replication and preventing membrane fusion. A recent study discovered that individuals who are homozygous for the C allele of the rs12252 SNP in the *IFITM3* gene experience more severe disease, with the severity increasing as they age [50]. In the Arab population, this genetic variant is also linked to increased COVID-19 mortality [51]. To date, genome-level association studies (GWAS) have detected four chromosomal regions potentially linked to severe COVID-19. One of these regions is situated on chromosome three, and it is known to contain six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1). However, the functions of these genes remain unexplored at present [52]. In addition, an international GWAS comparing hospitalized COVID-19 patients with the general population identified three additional regions that were previously discovered in a recent GWAS analyzing 2244 patients with critical illnesses from UK intensive care units (ICUs) [53]. The odds ratio for susceptibility alleles that are heterozygous ranges from 1.2 to 1.4. Out of these three regions, two of them also possess genes that play a role in the immune response against viruses. The first region, located at chr12q24.13, includes the OAS1, OAS2, and OAS3 genes, as well as a cluster of *ISG*s that are necessary for activating the RNase L enzyme. The second one, chr21q22.1, contains IFNAR2, which is responsible for encoding the second chain of the IFN receptor [53]. Contrary to expectations, recent data show that having more alleles of genes implicated in the type I IFN response is not beneficial against COVID-19. Individuals with Down syndrome, who have an extra chromosome encoding multiple genes related to the type I IFN response, such as triplicated IFN receptors in trisomic cells, initially experience an overactive type I IFN response, which may provide an advantage during the early stages of infection. However, this heightened response later leads to a harmful inflammatory response due to the pleiotropic effects of type I IFNs [54]. In addition to genetic defects, severe COVID-19 is also linked to the presence of autoantibodies against type I IFNs. Research revealed that a minimum of 10% of patients suffering from critical COVID-19 pneumonia possessed autoantibodies capable of neutralizing significant quantities of one or more type I IFN subtypes, both in vitro and in vivo. The IgG antibodies primarily exhibited specificity toward IFNω, IFNα, or both; however, a subset of individuals demonstrated autoantibodies against all 13 IFNα subtypes. Significantly, the presence of these autoantibodies was not observed in cases with SARS-CoV-2 who were asymptomatic or experienced minor symptoms. Furthermore, these autoantibodies were found to be present in just 0.33% of individuals who were in good health. Notably, the presence of these autoantibodies was observed in the patients prior to their infection with SARS-CoV-2, suggesting that they were the primary cause of the severe sickness rather than a result of the infection. The association between the existence of these antibodies and an unfavorable clinical result, as well as increased mortality rates, has been shown. It is noteworthy to state that a significant majority of the patients (94%)

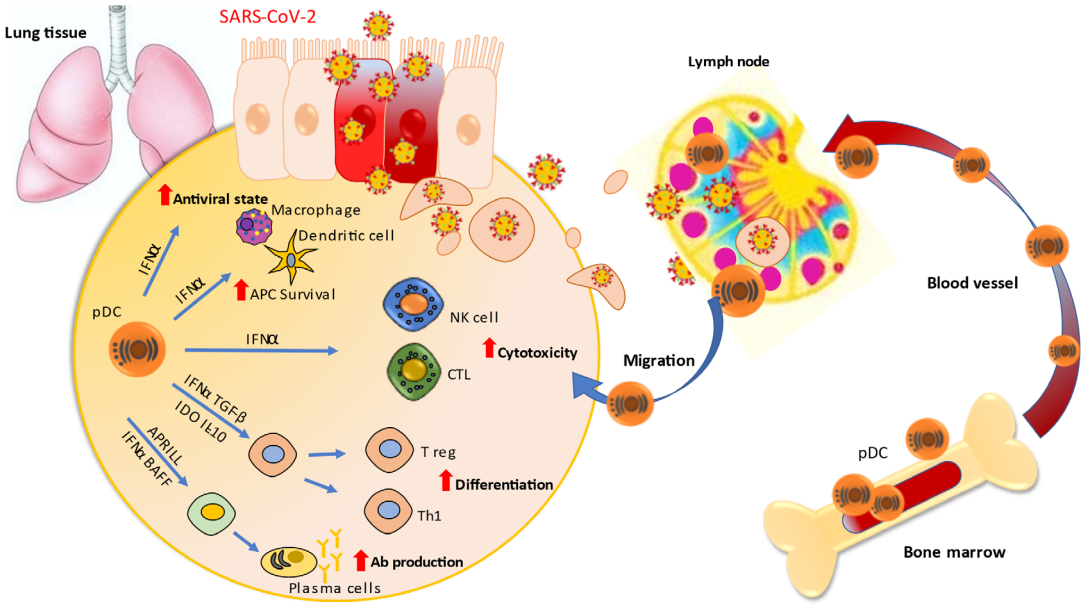

Figure 1. By producing type I IFNs from pDCs, SARS-CoV-2 infection is beaten

SARS-CoV-2 virus particles or cell debris derived from infected cells are delivered to draining lymph nodes when the virus breaches the first line of defense provided by the epithelial cells. The virus enters the draining lymph nodes and stimulates pDCs to migrate to the virus entry site. PDC-derived type I IFNs promote the activation of both innate and adaptive immune cells, blocking viral replication and inducing an antiviral response by triggering an antiviral state in the host cells.

Abbreviations: APRIL: A proliferation-inducing ligand; BAFF: B-cell activating factor; IL: Interleukin; IDO: Indoleamine 2, 3-dioxygenase; IFN: Interferon; NK: Natural killer; pDC: Plasmacytoid dendritic cell; TGF: Transforming growth factor; Th: T helper; Treg: T regulatory; CTL: Cytotoxic T ce.

exhibiting autoantibodies were of the male gender. Additionally, half of these patients were aged 65 or older, and a considerable proportion (more than one-third) of them experienced fatal outcomes as a result of COVID-19. The prevalence of autoantibodies against type I IFNs in individuals with severe COVID-19 is reported to be at least 3.5% among women and 12.5% among males [55]. A different study revealed that 16% of patients hospitalized in the ICU for non-viral respiratory infection had non-neutralizing anti-IFN antibodies detected in vitro. However, only severe SARS-CoV-2-infected patients showed detectable neutralizing autoantibodies, which were linked to elevated mortality rates and the onset of multiple organ failure [56]. In addition, Wang et al. conducted screenings on both COVID-19 patients and healthy individuals to detect autoantibodies targeting proteins that are secreted or found outside the cells. They discovered that 5.2% of the hospitalized COVID-19 patients had autoantibodies against type I IFNs. Additionally, they also detected autoantibodies against type III IFNs (IFNλ2 and IFNλ3). Patients with neutralizing antibodies against type I IFNs had a higher viral load on average, and experienced longer hospital stays [57]. It is important to mention that only a small percentage of individuals, specifically 2%, who have autoantibodies against type I IFNs also develop autoantibodies against IFNβ [55]. Nevertheless, it is probable that autoantibodies are more prevalent against the 13 subtypes of IFNα and IFNω. In addition, the genes responsible for some forms of IFN received significant negative selection, indicating their crucial involvement in the population's antiviral response [58]. The heightened production of autoantibodies is likely caused by a defect linked to the X chromosome. This is supported by the greater prevalence of this condition in men and the observation that one of the women who produced autoantibodies had a condition called incontinentia pigmenti, which is characterized by a non-random skewing of X chromosome inactivation [55]. Autoantibody generation becomes more probable after reaching the age of 65 due to alterations in the composition of the immune system that occur with aging. For example, a unique kind of B-cells called age-associated B cells (ABC) may develop, which thereafter transform into aberrant plasma cells that are characterized by an elevated production of autoantibodies [59]. Correspondingly, the prevalence of neutralizing antibodies significantly increases after reaching the age of 70. Neutralizing antibodies contribute to almost 20% of severe COVID-19 cases in individuals over the age of 80, as well as the overall number of fatal COVID-19 cases [60].

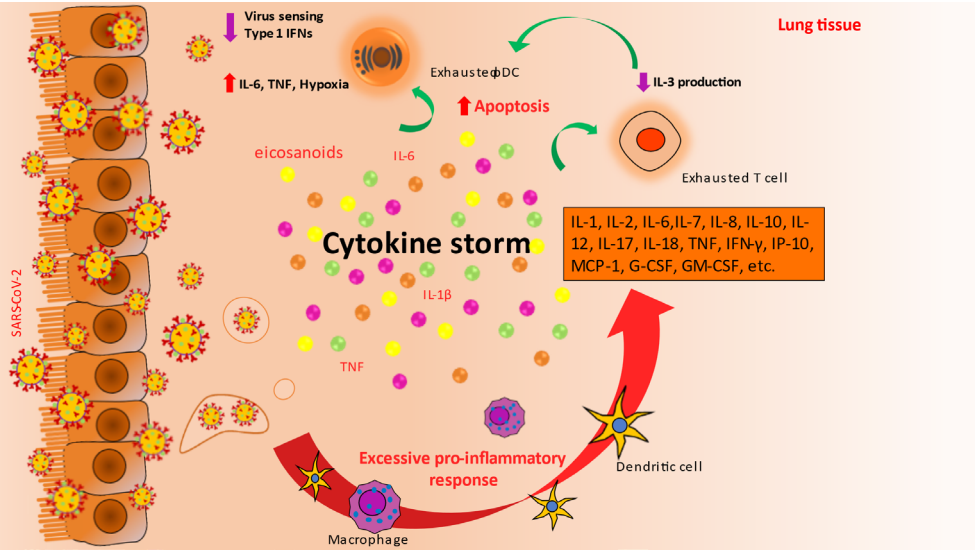

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Figure 2. Interferon type 1 production and inhibition of COVID-19 infection

Due to the overactivity of immune cells, severe COVID-19 generates excessive amounts of pro-inflammatory cytokines, which eventually result in cytokine storms. There is a high level of hypoxia and functional abnormalities in pDCs as a result of this inflammatory environment, which leads to pDC exhaustion. An inflammatory environment, however, inhibits pDCs from detecting viruses and producing type I interferons, and they produce pro-inflammatory cytokines, which can further enhance the detrimental inflammatory system. As a result of the excessive inflammatory milieu, T cells are also exhausted and die, leading to increased apoptosis. Apoptosis occurs as a result of the decrease in T cell-derived IL-3, an essential survival factor for pDCs. Consequently, severe COVID-19 leads to a reduction in pDCs.

Abbreviations: G-CSF: Granulocyte colony-stimulating factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN: Interferon; IP: Interferon gamma-induced protein, MCP: Monocyte chemoattractant protein; pDC: Plasmacytoid dendritic cell; TNF: Tumor necrosis factor.

The impact of biological sex and sex hormones on the antiviral interferon signature: Sexual dimorphism manifests in the physical attributes and behavioral patterns exhibited by males and females, as well as in the domain of autoimmune and antiviral immune responses [61]. It is widely recognized that women have a lower susceptibility to viral infection compared to men, owing to their capacity to generate a more efficient antiviral response. Regrettably, the present COVID-19 pandemic substantiates this fact, as it disproportionately affects men in a more severe manner compared to women. In COVID-19, the death rate is 1.7 times greater for men, and the inequalities between sexes are much more noticeable in individuals over the age of 30 [62]. A cohort longitudinal examination of COVID-19 patients revealed that female patients exhibited elevated levels of IFNα [63]. The distinct type I IFN-producing capacity of pDCs in males and females significantly influences this phenomenon. The genes responsible for the antiviral response are frequently found on sex chromosomes or possess a hormone response element (HRE), which means their expression is controlled by sex hormones and relies on the deactivation of sex chromosomes. The number of X chromosomes influences the type I IFN response of pDCs. In a mouse model with humanized characteristics, it has been demonstrated that when CD34+ human stem cells obtained from either females or males are transplanted into mice of corresponding sexes, pDCs derived from female stem cells generate greater quantities of type I IFNs when stimulated by TLR7 compared to pDCs from male donor cells, irrespective of the sex of the recipient mice. These studies indicate that the presence of two X chromosomes in women confers immunological advantages, potentially leading to a heightened immune response against IFNs [64]. A parallel investigation analyzed the impact of X chromosome count and sex hormones on the *TLR7*-triggered IFNα reaction of primary pDCs in healthy females, individuals with Turner syndrome, males, and transgender individuals undergoing hormone therapy. Research has revealed that the antiviral impact triggered by type I IFNs is significantly stronger in women who are in good health compared to men or women with Turner syndrome, a condition characterized by the absence of one of the X chromosomes. Nevertheless, there was no correlation between the intensity of the antiviral response and the levels of sex hor-

mones in the bloodstream [65]. Moreover, it is established that many genes encoded on the X chromosome, which are part of the TLR signaling system, have the ability to evade X chromosome inactivation. As a result, they play a role in enhancing the antiviral and humoral immune response. Studies have shown that *TLR7*, which is encoded on the X chromosome, is expressed from both alleles in pDCs, B cells, and monocytes of women (XX) as well as men with Klinefelter's syndrome (XXY). Furthermore, immune cells with biallelic *TLR7* expression exhibit higher levels of transcriptional activity compared to cells with monoallelic expression [66]. Another study has provided support for the notion that pDCs derived from women with biallelic *TLR7* expression exhibit a higher capacity for IFN production compared to pDCs expressing only one *TLR7* allele [67]. These statistics may possibly elucidate the reason for the elevated death risk for COVID-19 in men with a single X chromosome in comparison to women [67]. Women with biallelic *TLR7* expression may exhibit enhanced production of type I IFNs by their PDCs and demonstrate a more prompt response to SARS-CoV-2 infection. This heightened immune response may lead to improved management of the illness in women [67]. Recent research has provided additional evidence that a mutation in the *TLR7* gene on the X chromosome, which causes its function to be impaired, leads to severe symptoms of COVID-19 in young males. This finding suggests that the TLR7-mediated type I IFN response is crucial in combating the disease [48]. Furthermore, it is crucial to note that type I IFNs produced by plasmacytoid dendritic cells play a critical role in controlling B cell activation and promoting their transformation into plasma cells. Consequently, these interferons are indispensable for generating an optimal antibody response against viral infections. As a result, women may possess an advantage over men in terms of antibody response to SARS-CoV-2 infection [68]. Sex hormones exert an influence on the body's antiviral immunological responses. Steroid hormones can easily pass through cell membranes because they are lipophilic. Once within the cells, they connect to nuclear receptors and have an impact on the activities of immune cells, including pDC [69]. Oestrogen is recognized for its significant involvement in controlling TLR-mediated immune responses in human and mouse pDCs. Studies have shown that in mice, the hormone 17β-oestradiol (E2) has a notable effect on increasing the production of IFNα by spleen pDCs when stimulated by CpG-B [70]. Confirming this finding, administering E2 to postmenopausal women also notably augmented the production of IFNα by primary pDCs through the activation of TLR7/9. Additionally, research has demonstrated that E2 specifically affects pDCs by directly interacting with the oestrogen receptor α (ERα). This was confirmed when the favorable impact of E2 therapy on TLR-induced IFNα production was eliminated in pDCs from mice lacking ERα [71]. Furthermore, the disruption of oestrogen receptor signaling greatly diminishes the production of IFNα triggered by TLR7 in human pDCs derived from umbilical cord blood (104). A further investigation discovered that the ERα signaling pathway stimulates the production of higher levels of IFNα in TLR7-stimulated mouse pDCs by activating the transcription factor IRF5. This transcription factor acts as a positive regulator of the IFNα response in pDCs [72]. A solitary study has investigated the impact of androgens on the functionalities of pDCs. Research has demonstrated that dihydrotestosterone (DHT) can decrease the production of IFNα by pDCs, which are isolated from the blood of healthy women, through the inhibition of TLR7. Additionally, it was discovered that pDCs in male newborns exhibited a lower production of IFNα when stimulated by TLR7, in contrast to female infants. This difference can be attributed to the increase in testosterone that occurs in male children between 1 and 6 months after birth [73]. From the provided results, it can be inferred that estrogens have a beneficial impact on the type I IFN response of pDCs, while testosterone may have a detrimental influence on these processes. Hence, gender disparities can significantly influence the robustness of an individual's immune reaction to viral infections, as well as the effectiveness of vaccines [74]. Current observations indicate that COVID-19 poses a higher risk to pregnant women, potentially due to the impact of progesterone. Pregnant women exhibit a lower likelihood of experiencing common symptoms associated with SARS-CoV-2 infection, such as fever, difficulty breathing, and muscle discomfort. However, they have a higher probability of being admitted to the ICU or needing invasive ventilation compared to non-pregnant women of reproductive age. Additional risk factors for COVID-19, including as pre-existing comorbidities, ethnicity, chronic hypertension, pre-existing diabetes, high maternal age, and high body mass index (BMI), may pose the possibility of more severe viral infections during pregnancy. Pregnant individuals who contract COVID-19 face a heightened likelihood of experiencing preterm birth, gestational toxaemia, caesarean section, maternal mortality, and requiring admission to the ICU. Infants are also more prone to necessitate neonatal intensive care [75]. During pregnancy, various physiological alterations take place in the body, including modifications in the functioning of the immune system. In pregnant women, the immune response undergoes a change toward a

Th2 type tolerogenic immune response from the beginning of implantation. This immune response creates an ideal milieu in the maternal uterus for the development of the fetus. After pregnancy, there is a shift from the prevailing Th2 immune response to a Th1 dominance, which is necessary for the initiation of labor [76]. The quantity of circulating NK cells and pDCs diminishes as pregnancy advances [77]. Moreover, in vitro tests have already demonstrated that following H1N1 infection, pDCs from pregnant women exhibit reduced production of IFNα in comparison to non-pregnant women [78]. This phenomenon may elucidate the reason behind the heightened vulnerability of pregnant women to severe illness during influenza outbreaks and COVID-19 pandemics [79]. Progesterone hormone levels in women rise during pregnancy, and its immunosuppressive features and unfavorable effects on the functions of pDCs are widely recognized [80]. Unlike estrogen, progesterone and its synthetic analogs suppress the function of natural immune cells and have a detrimental impact on the production of type I IFNs in human pDCs [81]. In vitro investigations have demonstrated that both progesterone and depo-medroxyprogesterone acetate (DMPA), a synthetic version of progesterone, prevent the release of IFNα in mouse and human pDCs by inhibiting the activation of TLR9. Research has demonstrated that in vivo infection with vesicular stomatitis virus (VSV) notably reduces serum IFNα levels in mice treated with DMPA, in comparison to mice not treated with DMPA. Progesterone's inhibitory action may arise from its ability to restrict the nuclear translocation of the transcription factor IRF7 in pDCs, which is stimulated by TLR9 activation [82]. The observations suggest that pregnant women are more susceptible to viral infections, including SARS-CoV-2, due to the increased tolerogenic responses that protect the fetus during pregnancy and the inhibitory effect of progesterone on the generation of type I IFNby pDCs. One issue is whether type 1 IFN therapy is safe for pregnant women. A meta-analysis determined that the use of IFNα during pregnancy did not result in a substantial increase in developmental abnormalities, miscarriages, stillbirths, or preterm deliveries among women who were exposed to IFNs [83]. Thus, in pregnant women suffering from severe COVID-19, if the possibility of IFN therapy arises, it may be safe to use.

The impact of aging on reduced IFN production

One of the main clinical risk factors for COVID-19 mortality is age [84]. This is supported by the finding that patients under 60 years of age had a lower COVID-19 death rate (1.4%) than patients over 60 years of age (4.5%) [85]. A shift in the innate immune system toward inflammation, age-related cellular alterations, and irregularities in antiviral signaling pathways, which results in extended, delayed type I IFN production are likely the causes of increased morbidity and death in the elderly. As previously mentioned in the case of SARS-CoV infection, the underlying inflammatory phenotype in the elderly may induce a delayed type I IFN response following viral infections [86]. Severe COVID-19 is characterized by a cytokine storm and enhanced tissue damage due to a postponed antiviral type I IFN response [87]. Regarding SARS-CoV infection, disruption of IFN production may cause a shift in the frequency of pro-inflammatory and alveolar macrophages in the lung [88]. Moreover, during viral infections, type I IFNs stimulate the activation of natural killer (NK) cells while blocking the pathogenic reactions that are carried out in the infected mucosa in both neutrophil granulocytes and type II innate lymphoid cells (ILC2) [89]. Moreover, as people age, the efficacy of the early type I IFN response declines because fewer DCs and macrophages produce IFN and because signaling pathways involved in IFN production are impaired [90]. As individuals age, there is a decrease in the number and effectiveness of pDCs, whereas the myeloid dendritic cell (DC) population remains constant [91].

The reduced ability of pDCs to produce IFN in older individuals is partially caused by the decreased expression of Toll-like receptors 7 and 9 (TLR7/9) and the impaired functioning of interferon regulatory factor 7 (IRF7) [92]. The observed cell damage in aged cells is linked to elevated amounts of reactive oxygen species (ROS) resulting from these activities [93]. In addition, the process of aging also affects the RIG-I/MDA-5 signaling pathway. This is because the degradation of TRAF3 by proteasomes is heightened in older human monocytes. As a result, the activation of IRF3 becomes less effective, leading to a decrease in the generation of antiviral interferons [94]. Unlike adults, children have a high abundance of receptors, such as RIG-I and MDA5 in their nasal epithelial cells, macrophages, and DCs. The elevated baseline synthesis of these sensors leads to a more robust and early antiviral response to SARS-CoV-2, which can partly account for the reduced susceptibility of children to the more severe manifestations of COVID-19 [95]. Consequently, the diminished ability of aged adults to produce type I IFN, the delayed response of interferon, and the malfunction of pDCs significantly decrease the chances of successfully overcoming SARS-CoV-2 infection [96].

The impact of microbiome on the production of antiviral IFN

An intact and well-functioning gut microbiota is crucial for reinforcing the immune system of the host. Firstly, it inhibits the initiation of pro-inflammatory processes, while simultaneously priming the body for subsequent viral infections [97]. Nevertheless, during dysbiosis, these defensive functions are compromised. Multiple studies have indicated a potential correlation between gut dysbiosis and the clinical presentation and severity of COVID-19 [98]. Moreover, infection with SARS-CoV-2 can also modify the microbial content of the lung, indicating the presence of significant inflammation in lung tissues. The degree of inflammation observed in the lung had a strong correlation with the quantities of disease-causing microorganisms and the SARS-CoV-2 virus [99]. The respiratory tract of hospitalized COVID-19 patients may become dysbiosis, which worsens over time and is associated with the severity of the disease and activation of the immune system [100]. An increase in the presence of *Staphylococcus* species might be found in individuals who are intubated. In addition, the tiny commensal DNA viruses, Anelloviridae and Redondoviridae, exhibited heightened levels and presence in severe cases of COVID-19 [100]. Within the upper respiratory tract, there was a continuous rise in both the amount and diversity of bacteria. In addition, the presence of a type of bacteria called Corynebacterium (unclassified) increased. The level of ASV0002 declined in proportion to the severity of the condition [101]. COVID-19 patients experienced a decrease in the presence of beneficial immunomodulatory gut bacteria, including *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *bifidobacterium* species. This reduction persisted even after a 30-day recovery period from COVID-19. The decrease in beneficial gut bacteria showed a correlation with heightened disease severity, as well as enhanced concentrations of inflammatory indicators and cytokines in the plasma of the patients. This implies that the ongoing disruption of microorganisms following the remission of the disease may play a role in post-COVID syndrome [102]. A study also observed a reduction in beneficial commensal species and an increase in potentially harmful opportunistic pathogenic species in the gastrointestinal tract of individuals with COVID-19. The presence of *Burkholderia contaminans,* Bacteroides *nordii*, and *Blautia sp*. CAG 257 was found to be strongly correlated with severe disease. There was a positive correlation between the prevalence of Burkholderia contaminans and increased inflammation, as well as a decrease in the number of immune cells [103]. Furthermore, COVID-19 patients with intestinal dysbiosis have exhibited a reduction in *Lactobacillus* and *Bifidobacterium* species. These species are crucial in safeguarding against intestinal infections by triggering intestinal functions, enhancing immune responses, and preventing the proliferation of harmful species [6]. The commensal microbial flora plays a crucial role in maintaining the baseline secretion of IFN in the human body. If there is an imbalance in the microbial flora (known as dysbiosis), it might result in a weakened immune response against viral infections. The immune and stromal cells are continuously prepared to fight against viruses due to the activating signals received from commensal bacteria. They are responsible for maintaining the continuous, basal production of IFN by pDCs, among other functions [104], the baseline activity of mononuclear phagocytes and NK cells [105], the baseline production of IFN by lung stromal cells, and thus the constitutive expression of antiviral Mx proteins [25]. It is crucial to acknowledge that antibiotic treatment can readily disrupt this fragile system, as antibiotics not only attack harmful bacteria but also eliminate or significantly decrease the population of beneficial bacteria, which play a role in maintaining consistent levels of IFN signals. Consequently, antibiotics eradicate the body's natural antiviral state [106] and enhance the susceptibility to viral infections and inflammatory disorders [107]. This phenomenon was effectively illustrated using a mouse model. When mice possessing a robust population of beneficial microorganisms in their intestines were exposed to the influenza virus, a notable 80% of the mice managed to survive.Nevertheless, when mice were given antibiotics before the infection, only 33% of them survived. However, the transplantation of fecal matter was able to save the mice from death or sepsis caused by the pathogen. The data suggest that a well-functioning intestinal flora offers robust defense against influenza, as the body's systemic antiviral immunity, powered by the gut microbiota, was already active upon virus entry. Conversely, when there are no intestinal bacteria, the antiviral genes are only activated when the immune response is stimulated. However, this occasionally occurs belatedly, after the virus has already replicated in the body, resulting in a substantial viral load that triggers an excessive and harmful immune response [25]. Consequently, a notable association was discovered between prior antibiotic usage and heightened severity of COVID-19 in Spain [108]. Therefore, it may be inferred that dysbiosis resulting from excessive antibiotic usage can be classified as a risk factor for severe COVID-19, among various other variables. These data indicate that using probiotics as a preventive measure may be recommended to decrease the occurrence of respiratory infections [109]. Multiple pieces of evidence suggest that prebiotics and probiotics can boost the type

I IFN response of pDCs by stimulating TLR9, resulting in a more efficient antiviral response [110]. In addition to probiotics, it may be wise to enhance the consumption of anti-inflammatory meals, such as vegetables and fruits, as a diet rich in fiber provides beneficial bacteria with a valuable source of carbohydrates. Furthermore, foods that include a substantial amount of polyphenols, such as vegetables, fruits, cereals, tea, coffee, dark chocolate, or cocoa powder, possess prebiotic or antibacterial characteristics. As a result, they can effectively impede the reproduction of harmful microorganisms within the body [111]. Hence, using an appropriate, tailored diet could potentially serve as a preventive measure against coronavirus infection and aid in the recuperation of patients. Additionally, it may assist in reducing dysbiosis resulting from the infection and restoring the gut microbiota post-recovery from COVID-19.

Obesity and antiviral IFNs

Obesity increases the chance of experiencing a more severe progression of SARS-CoV-2 infection [112]. Obesity is widely linked to diabetes, hypertension, and coronary disorders, all of which are risk factors for COVID-19. For instance, a study revealed that 74% of individuals with diabetes were obese, potentially intensifying the gravity of COVID-19 within this particular population [113]. The co-occurrence of obesity, diabetes, hypertension, and dyslipidemia is referred to as metabolic syndrome, a medical condition that is also linked to higher mortality rates in COVID-19 cases [114]. Obesity is not only one risk factor, but it can also interact with other underlying conditions to enhance the risk of severe SARS-CoV-2 infection. Based on an extensive analysis of data from 5700 individuals who were admitted to the hospital with SARS-CoV-2 infection, it was found that obesity (41.7%) was the second most prevalent underlying health condition in COVID-19, following hypertension (56.6%) (169). Based on a study conducted in France, 47.6% of patients in the ICU had a BMI exceeding 30 kg/m^2, while 28.2% had a BMI exceeding 35 kg/m^2 [115]. Findings from two Spanish ICUs have also verified that obesity is the prevailing comorbidity, affecting 50% of hospitalized patients [116]. However, statistics obtained from six hospitals affiliated with New York University revealed a negative connection between BMI and age among individuals referred to the ICU. While the risk of severe illness in SARS-CoV-2 infection rises with age, younger individuals with critical illness exhibited a higher prevalence of obesity [117]. A meta-analysis revealed that those who are obese have a 113% higher chance of being hospitalized, a 74% higher risk of being admitted to an ICU, and a 48% higher risk of mortality [118]. Obese cases may experience more severe symptoms of COVID-19 due to a diminished and prolonged type I IFN response, leading to a reduced antiviral immune response. Obese individuals exhibit elevated serum levels of the hormone leptin, which suggests the presence of leptin resistance. Leptin can stimulate the production and stimulation of suppressor of cytokine signaling (SOCS), while simultaneously reducing the type I IFN response in cases who are fat [119]. Both type I IFNs and leptin utilize the JAK-STAT signaling pathway, which can be suppressed by SOCS3. This suppression leads to a reduced IFN response to viral diseases in cases who are obese [120]. Recent evidence demonstrates that the baseline expression of SOCS3 is elevated and is associated with a diminished type I IFN response in individuals with obesity [121]. Obese individuals are more prone to infections and have a higher fatality rate during seasonal influenza outbreaks [122]. Furthermore, obesity is associated with elevated levels of inflammatory cytokines, heightened polarization of lung macrophages toward the M1 phenotype, and compromised IFN response and induction of *ISG*s in respiratory epithelial cells and macrophages. These factors collectively contribute to the development of more severe pneumonia and lung damage in obese individuals [123]. Moreover, obese patients typically consume a diet that is rich in fat, which might contribute to dysbiosis. This, in turn, reduces the strength of the type I IFN response [118]. Obese people have decreased production of IFN, which may provide an environment conducive to the development of new, highly infectious strains of the virus [123].

Chronic medical conditions that compromise the immune system by impairing the interferon response

As previously stated, chronic disorders, such as diabetes, hypertension, and obesity are commonly identified as the primary cause of death in the majority of COVID-19 cases. However, the prevalence of immunosuppression-associated chronic illnesses, resulting from either internal immune system dysfunctions or immunosuppressive medications, is also notably elevated [123]. This category encompasses several conditions, such as primary and secondary immunological deficiencies, malignancies, chronic renal failure, post-transplant organ status, and autoimmune illnesses. Special emphasis should be placed on this category of illnesses since both the patients themselves and anyone in close proximity to them are at a heightened risk. Immunosuppressed individuals can act as “reservoirs” for viruses and may remain contagious for several months [10]. Moreover,

it is worth noting that viral pneumonia might manifest atypically in these individuals, with modest levels of inflammatory markers initially, but later, it can be linked to a more severe progression of the disease [125]. Research has indicated that individuals with primary and secondary immunodeficiencies experience higher rates of sickness and death from COVID-19 compared to the general population [126]. A meta-analysis further confirms that individuals with chronic renal failure who undergo immunosuppression are at a higher risk of mortality [127]. The probability of being admitted to ICU and needing mechanical ventilation is 3.5 times higher in cancer patients who have COVID-19. They are also more susceptible to infections with SARS-CoV-2 and take longer to eradicate the virus from their body relative to the general population [5]. However, autoimmune illnesses present a more complicated issue. COVID-19 is more severe than influenza in autoimmune people [128]. Low-dose immunosuppressive medication seems to offer protection against the consequences of COVID-19 in these individuals [129]. Immunosuppressive medications employed for the treatment of specific autoimmune disorders also affect the generation of type I IFNs and the activities of pDCs, perhaps increasing the susceptibility to more serious viral infections. For instance, studies have shown that steroids can decrease the number of pDCs and their type I IFN responses in patients with systemic lupus erythematosus (SLE). However, it is crucial to highlight that once glucocorticoid treatment is stopped, both the pDC count and IFNα levels in these patients quickly return to normal [130]. Hydrochloroquine decreases the production of type I IFNsby pDCs that are activated by TLR7 or TLR9 in patients with SLE [131] Additionally, it suppresses the generation of type I IFNs by pDCs in individuals with cutaneous lupus erythematosus via inhibiting the activation of TLR9 [132]. In addition, mycophenolic acid, the active form of mycophenolate mofetil, can effectively decrease the release of type I IFNin pDCs of patients with SLE. This reduction occurs in a dose-dependent manner and is achieved by preventing the movement of IRF7 into the cell nucleus [133]. Moreover, baricitinib, a substance that hinders the JAK/STAT pathway, has the capability to impede the secretion of IFN by pDCs, thus heightening the probability of varicella reactivation [134]. It is crucial to acknowledge that in addition to the immunomodulatory effects stated earlier, several inhibitors of the interferon response also demonstrate direct antiviral activity. Chloroquine disrupts various phases of the viral life cycle, such as viral entrance, uncoating, assembly, and budding. Chloroquine prevents the fusion of the virus with the endosome by raising the pH of the endosome. Additionally, it can hinder the alteration of viral proteins after they are produced by interfering with proteolytic activities [135]. Furthermore, mycophenolate mofetil could suppress the replication of SARS-COV-2 in laboratory conditions. Calcineurin and mTOR inhibitors, together with thiopurine analogs, had comparable antiviral efficacy against both SARS-CoV and MERS-CoV strains [136]. However, immunosuppressive drugs can be harmful during the early stage of COVID-19 as they hinder the compromised immune system from effectively managing viral replication. Nevertheless, during the advanced phases of the illness, the immunosuppressive properties of these medications can be very advantageous by averting an excessive immune reaction, the occurrence of cytokine storm, and the failure of many organs. Therefore, as mentioned earlier, the administration of low doses of immunosuppressive drugs may be beneficial for people with autoimmune conditions, as it can reduce the severe symptoms of COVID-19 caused by an overactive immune system [129].

2. Conclusions

In conclusion, we explored the role of type I IFNs and pDCs in COVID-19 severity. Individuals with a weaker type I IFN response and lower levels of pDCs are more likely to have a severe disease outcome. Factors, such as genetic deficiencies, autoantibodies against type I IFNs, chronic illnesses, dysbiosis, obesity, and immunosuppression contribute to impaired IFN responses and increased COVID-19 severity. Understanding the dysregulation of type I IFNs and pDCs in COVID-19 is important for developing strategies to manage and treat the disease. Additionally, factors, such as sex, age, and hormonal influences also impact the immune response and disease outcomes in COVID-19. This research highlights the need for optimized IFN therapies, considering the timing, dose, and route of administration, to reduce disease severity and mortality. Overall, this information provides important insights into the immune response to SARS-CoV-2 and can contribute to the development of effective strategies to control and prevent severe COVID-19. Further research in this field may help improve risk assessment and patient management in the future.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization, methodology and investigation: All authors; Methodology: Mohammad Reza Ghazanfari. Niki Ghambari Mohammadi; Supervision and writing original draft: Bahman Rahimlou and Mohammad Reza Ghazanfari; Review & Editing: Mohammad Reza Ghazanfari and Niki Ghambari Mohammadi; Supervision: Bahman Rahimlou, Mohammad Reza Ghazanfari.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgements

The authors thank the many investigators in the coronavirus and interferon fields for their contributions that made this review possible.

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