Review

Off balance: Interferons in COVID-19 lung infections

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A R T I C L E   I N F O

Article History:
Received 31 March 2021
Revised 14 September 2021
Accepted 7 October 2021
Available online 19 October 2021

Keywords:
Interferons
Cytokine Storms
SARS-CoV-2
COVID-19
TNFα

A B S T R A C T

Interferons are innate and adaptive cytokines involved in many biological responses, in particular, viral infections. With the final response the result of the balance of the different types of Interferons. Cytokine storms are physiological reactions observed in humans and animals in which the innate immune system causes an uncontrolled and excessive release of pro-inflammatory signaling molecules. The excessive and prolonged presence of these cytokines can cause tissue damage, multisystem organ failure and death. The role of Interferons in virus clearance, tissue damage and cytokine storms are discussed, in view of COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The imbalance of Type I, Type II and Type III Interferons during a viral infection contribute to the clinical outcome, possibly together with other cytokines, in particular, TNFα, with clear implications for clinical interventions to restore their correct balance.

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Introduction

Interferons (IFNs) are essential cytokines that mediate the host resistance response to viral infections. In the absence of IFNs or compromised cellular programs induced by IFNs, vertebrates may be susceptible to lethal viral infections. There are 21 human IFNs, classified in 3 types (16 Type-I: 12 IFNαs, IFNβ, IFNε, IFNκ, and IFNω; 1 Type-II, IFNγ; and 4 Type-III, IFNλ1, IFNλ2, IFNλ3, and IFNλ4), involved in innate and adaptive immune responses against not only to viruses but also to other pathogens as well as to tumors and in tissue repair. In general, the production of distinct IFNs depends on the cell type and is stimulated during viral infection when the viral nucleic acid in the cytoplasm is detected by intracellular pattern recognition receptors (PRRs). Then, the produced and secreted IFNs will bind and activates heterodimeric receptors (IFNRs) on the cells in autocrine and paracrine mechanisms that initiate a complex cascade of signaling, culminating in transcription of hundreds of different Interferon-Stimulated Genes (ISGs) resulting in strong antiviral innate and adaptive immune responses [1-3].

Briefly, Type I and III IFNs bind to their heterodimeric receptors activating the JAK/STAT pathway, which in turn activate the heterotrimeric transcription factor complex ISGF3, which consists of phosphorylated STAT1/STAT2 and IRF9. However, unphosphorylated STAT molecules and IRF9-STAT2 homodimers have also been described [4]. Type II IFN also signals through the JAK/STAT pathway, resulting in the formation of phosphorylated STAT1 homodimers, also known as IFNγ-activated factor (GAF). Activated ISGF3 and GAF, resulting respectively from type I/III and type II IFN actions, translocate to the nucleus and bind IFN-stimulated response elements (ISRE) and gamma-activated sequences (GAS), respectively, in the promoter regions of ISGs (Figure 1). In this review, we will discuss the recent data showing the association of COVID19 severity with the correct balance between the IFN types and other cytokines for a favorable clinical outcome during infection by SARS-CoV-2.

Coronaviruses (CoVs) are viruses belonging to the family Coronaviridae, with a large positive-sense single-stranded RNA that cause diseases in humans and animals. The new SARS-CoV-2 was identified as a beta-coronavirus responsible for the pandemic COVID-19 (Coronavirus Disease 2019) [5]. Patients with severe COVID-19 present high concentrations of proinflammatory cytokines and chemokines in the plasma, massive infiltration of monocytes and neutrophils (Figure 2).

Types of Interferons (IFNs)

IFNs are components of the innate and adaptive immune systems. Type I IFNs are produced by many cell types including lymphocytes (NK cells, B-cells and T-cells), macrophages, fibroblasts, endothelial cells, osteoblasts, leukocytes, plasmacytoid and dendritic cells [6]. Type II IFN is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response, and by CD4+ and CD8+ T cells of the adaptive immune cells [7]. While the main producer of Type III IFNs are type 2 myeloid dendritic cells, epithelial cells and hepatocytes [8,9], the receptors for Type I and Type II interferons are expressed ubiquitously on almost all nucleated cells and Type III interferon receptors are expressed on epithelial, dendritic cells and neutrophils. The antiviral effects of IFNs are dictated

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https://doi.org/10.1016/j.ebiom.2021.103642
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EBioMedicine 73 (2021) 103642

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom
by the presence of producer cells and responder cells with IFN receptors. For instance, Type III IFN receptors are restricted to epithelial cells in gastrointestinal, respiratory and reproductive tracts, they are considered as the first line of defense against viruses at these sites [10]. In contrast, all nucleated cells express Type I and II IFN receptors. 

**Types I and III IFNs in COVID-19**

SARS-CoV-2 infects lung alveolar epithelial cells and these cells die due to the virus' cytopathic effect as viral replication proceeds. Recovery is achieved by proliferation and differentiation of neighboring progenitor epithelial cells. During viral infections, Type I and Type III IFNs are important mediators of the innate immune responses triggered by the recognition of pathogen-associated molecular patterns (PAMPs) by the PRRs of the cell [11]. Type I IFNs are more proinflammatory when compared to Type III IFNs [10]. Surprisingly, although both Type I and Type III IFNs have antiviral activities, mice infected with influenza virus have increased susceptibility to pneumonia caused by *Staphylococcus aureus* or *Streptococcus pneumoniae* that were associated with the increase in IFNα production or IFNα treatment [12-15]. Similarly, IFNα mRNAs were observed in bronchoalveolar fluid and naso-oropharyngeal samples of SARS-CoV-2 patients and increases in IFNα mRNA expression were positively associated with increases in COVID-19 disease morbidity [16]. Interestingly, increases in IFNλ stimulate apoptosis and expression of tumor suppressor p53 that impairs proliferation, differentiation and repair of the lung epithelial cells, increasing disease severity, lung damage and susceptibility to bacterial superinfections (Figure 3F-G) [16,17]. Although Type I IFNα and IFNβ also reduces lung epithelial cell proliferation after treatment during influenza, only IFNα compromises lung epithelial tissue recovery [17]. Moreover, Type I IFN production and activity were highly suppressed in severe COVID-19 patients. These patients present a proinflammatory picture driven by nuclear factor-κB (NF-κB) and characterized by increased IL-6 and TNFα [18]. The reasons for this impaired production, signaling and activity of Type I IFN seems to be related, at least in part, to inborn errors associated to Type I IFN signaling cascade or production of autoantibodies, especially to IFNα and IFNβ [19-21]. In addition, it was also shown that the presence of autoantibodies against Type I IFN (IFNα and IFNβ) was proportionally higher in males and elderly with severe COVID-19 [20,21]. Altogether, these data suggest an important
role of these IFNs in protection and susceptibility to severe pneumonia in COVID-19.

Viral proteins targeting IFN antiviral response

There are many clinical similarities between severe influenza and COVID-19. The COVID-19 clinical manifestations include profound and uncontrolled inflammatory response, massive cytokine release, diffuse alveolar damage and lung infiltration with inflammatory cells, most of them comprised of neutrophils. However, there are also striking differences, related to thrombosis and endothelial dysfunction in COVID-19, which appears to exceed in influenza patients as observed from lung pathology of fatal cases [22,23].

Both influenza and SARS-CoV-2 have virulence factors targeting the IFN antiviral responses. Influenza hemagglutinins have been shown to facilitate ubiquitination and degradation of Type I IFN receptors, thus reducing the expression levels of Type I IFN receptors and impacting the strength of their responses and ISGs expressions [24,25]. Besides this, the non-structural protein 1 (NS1) inhibits the TRIM25, a RING-finger E3 ubiquitin ligase, blocking RIG-I-mediated innate immunity and suppression of host IFN response. Furthermore, NS1 also inhibits the production of Type I IFNs and downstream effector molecules of IFNs-mediated signal transduction processes by the inhibition of protein kinase RNA-activated (PKR) through the increased expression of host small non-coding RNAs (vault RNAs). As a result, the replication and production of virus particles are also increased [25,26]. NS1 may also affect the phosphorylation of IκB kinases (IKK) and decrease the NF-κB complex in the nucleus and the gene expression mediated by NF-κB. The JAK-STAT pathways of IFNs are also impaired by NS1 that lowers the phosphorylation levels of STAT1, STAT2 and STAT3, preventing proper transcription of ISGs [27]. The transcription of genes is also affected by direct binding of NS1 to host double stranded DNA [28]. Therefore, NS1 is a master key to block the innate immune system, the transcription of IFNs and ISGs through many mechanisms but also of the adaptive immunity by modulating the dendritic cells capacities to induce the T cell responses [29,30]. However, besides NS1, other influenza proteins help to evade Type I IFN actions. PB1-F2 and PB2 influenza viral proteins also interfere with Type I IFN signaling pathway through interaction with MAVS in the mitochondria [31-33]. M2 protein from influenza also affects the generation of IFNs by blocking the host autophagy and TLRs pathways [34].

Although SARS-CoV-2 deregulates cell signaling pathways to generate a permissive environment for viral replication, mainly related to delayed hyperinflammation, generating weakened and delayed IFN responses [35], it was observed that the Spike protein (S) amplifies the activation of IFNα and the Envelope protein (E) stimulates the transcription of ISGs, in an opposite direction of creating a permissive milieu for SARS-CoV-2 [36]. The Membrane protein (M) and the Nucleocapsid (N) structural proteins inhibits the activation of IFNβ by Type I IFN signaling pathway [36,37]. NSP1 inhibits STAT1 phosphorylation upon IFNα stimulation as well as the IFNβ production in HEK293T cells [36,38]. In contrast, NSP2 accelerates the activation of IFNβ [36]. NSP3, NSP12, NSP13, NSP14, ORF3, ORF6, ORF7 and ORF8 proteins inhibit Sendai virus-induced IFNβ promoter activation, IFNα downstream signaling or NF-κB-responsive promoter [35-39]. ORF9 protein targets the nuclear factor κB (NF-κB) essential modulator NEMO and interrupts its KG3-linked polyubiquitination upon viral stimulation, thereby inhibiting the canonical κB kinase alpha (IKKα)/β/γ-NF-κB signaling and subsequent IFNβ production [40].

Thus, viral proteins in general have diverse roles in disruption of cellular programs to evade and to weaken the host immune response [41] including Influenza and SARS-CoV-2 proteins, most of them as negative effectors targeted to Type I IFN pathway, though positive effectors can also be observed, as in the case of Spike, Envelope and NSP2 viral proteins as discussed above.

Type II IFN in COVID-19

Type II IFN is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response, and by CD4+ and CD8+ T cells of the adaptive immune cells [7]. Upon virus infection, IFNγ acts directly on CD8+ T cells to help them to
Figure 3. --- Respiratory tract infection by SARS-CoV-2. Infection occurs at the epithelial cells of the respiratory tract and the infection may be inhibited by pre-existing cross-reactive antibodies resulted from previous infections with seasonal viruses (A). The infection causes inflammation in the respiratory tract with the secretion of proinflammatory cytokines (B), activation of the endothelial cells (C) and expression of NK receptor ligands (MICA/B, MHC class I chain related protein A or B) on respiratory epithelium (C). The activated endothelium promotes the infiltration of NK-like T cells expressing NK (Natural Killer) receptors (NKR) exemplified by NK2DD on the cell surface from the capillaries (D) to the respiratory tract epithelium. The infiltrating NK-like T cells binds to NKR receptor ligands (MICA/B) and induce TCR-independent killing of epithelial cells expressing the NKR ligands (E). In response to viral infections, epithelial cells secrete Type I or Type III IFNs. In severe cases of the diseases, the presence of autoantibodies against IFNα and IFNβ (F) was observed and associated with higher morbidity, resulting in more viral infections. It was also observed an increase in the secretion of Type III IFN (IFNλ) (F). IFNλ impairs lung epithelial cell proliferation and tissue repair mediated by the expression of the tumor suppressor p53 gene and protein pathway. Cell death programs (PANoptosis) induced by cytokine storms, in special by IFNα and TNFα, perpetuates the local cytokine storms killing more epithelial cells in the respiratory tract (G) and the cytokine storms propagate (H) to other organs and tissues, provoking cytokine shock syndromes. Acute respiratory distress syndrome (ARDS) will be observed in the patient due to lung damage as well as multi-organ failures (I) due to systemic spread of the proinflammatory cytokines, in special of IFNγ and TNFα. The cytokine shock syndromes can be identified by clinical markers as listed in the figure (J). Susceptibility to bacterial superinfections is increased in damaged respiratory tract (K) due to cell killings by NK-like T cells (E) and by PANoptosis (G) in concert with inhibition of epithelial cell proliferation and repair by IFNγ (F). Cytokine shock syndrome markers: RBC, red blood cells; HCT, hematocrit; Hb, hemoglobin; PCT, Procalcitonin; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST; aspartate aminotransferase; BUN, blood urea nitrogen. (Figure created with BioRender.com).

Differentiate into cytotoxic T lymphocytes (CTL), which produce cytokines and effector molecules to restrict viral replication and kill virus-infected cells [42] as well as for the increase in CD4+ and CD8+ memory cells [43]. In general, type II IFN connects the innate immune response with the activation of the adaptive immune response [41]. The role of IFNγ during the infection of SARS-CoV-2 is beginning to be elucidated. It was shown that IFNγ is produced in high amount in patients with severe COVID-19 besides other proinflammatory cytokines. This Type II IFN is found in the serum of these patients and released in the culture medium when peripheral blood mononuclear cells (PBMCs) are infected with SARS-CoV-2 [44]. However, from the ten different cytokines that have their concentration increased in moderate to severe COVID-19 patients (IL-6, IL-18, IFNγ, IL-15, TNFα, IL-1β, TNFβ, IL-33, IL-2), only the combination of IFNγ and TNFα induced inflammatory cell death characterized by pyroptosis, apoptosis and necroptosis in bone marrow-derived macrophages (BMDM), a process known as PANoptosis [44] (Figure 3A-J). Neither IFNγ nor TNFα alone or in combination with the other inflammatory cytokines were able to induce this response. Interestingly, combination of IFNγ and TNFα provoked a lethal cytokine shock in mouse model that was completely abolished by IFNγ and TNFα blockade by neutralizing antibodies [44]. Though these results associate the important role of IFNγ and TNFα combination in the cytokine storm and acute lung damage with patient mortality as observed in severe cases of COVID-19, recent results also associate recovery-like stage of patients with enhanced TNFα and IFN-γ gene expression [45]. Therefore, the role of these cytokines in COVID-19 has to be confirmed in future studies.

COVID-19 severity in male and older people is associated with exacerbated inflammation in the respiratory tract

COVID-19 mostly induces mild to moderate clinical symptoms in younger patients. However, SARS-CoV-2 causes higher morbidity and mortality in older patients, with exacerbated inflammation of their respiratory tracts [46,47]. Interestingly, older healthy individuals present a chronic low-grade sterile systemic inflammation (an inflammatory response not induced by a pathogen), a process known as inflam-aging, with a higher baseline concentration of C-reactive protein (CRP) and some pro-inflammatory cytokines (IL-1β, IL-6, IL8). The mechanisms that lead to pro-inflam-aging are not completely understood but may involve impaired clearance of dead and dying cells with sustained inflammation, misfolded proteins, compromised gut barrier function, obesity and senescent cells which no longer divide but keep secreting pro-inflammatory cytokines, chemokines, growth factors and matrix metalloproteinases (MMPs), causing organ dysfunction during the aging process [48-51]. Interestingly, individuals in the same age group that do not present the inflam-aging profile are healthier and live longer when compared with those with the inflam-aging signs [48]. Although inflammation is essential to modulate both innate and adaptive immune response at the initial phases of immune stimulation, the inflammatory process is actively regulated by many processes, including the clearance of dead and dying cells and other mechanisms [49]. An excessive and non-resolved inflammation can inhibit antigen-specific immunity in vivo, as shown in the case of viral cancers [52].
It is also compelling that the inflamm-aging phenotype may contribute in exacerbating the hyperinflammation observed in older COVID-19 patients. The inflammation in the lungs of COVID-19 patients may involve the infiltration of monocytes, induction of Natural Killer Receptor (NKR) ligands (MICA/B) by cytokines produced in non-lymphoid cells [53], such as the pulmonary respiratory epithelial cells. These cells can be targeted and killed by NK-like T cells, possibly contributing to the pulmonary tissue damage in COVID-19 patients (Figure 3A-E) [47]. In contrast, NK cell production and proliferation in elderly is reduced and in elderly patients with COVID-19, the NK cells present in addition, an exhausted phenotype which affects the host defense against the SARS-CoV-2 acute infection in addition to the increased secretion of inflammatory cytokines [54,55].

Recent data showing that preexisting antibodies against seasonal human coronavirus able to cross-react with SARS-CoV-2 may also account for the clinical differences observed in children and adolescents versus elderly [56-58]. Children and adolescents are more recurrently infected by seasonal coronaviruses than elderly [58] and they present the highest amounts of cross-reactive antibodies between seasonal coronaviruses and SARS-CoV-2. Therefore, it is conceivable that sustained infection by seasonal coronavirus in children and adolescents induces protective cross-reactive antibodies and these preexisting antibodies influences the severity of COVID-19 by SARS-CoV-2 infection, in contrast to elderly. It is also possible that both mechanisms, inflamming and preexisting antibodies influences the clinical outcome differences observed in children, adolescents and elderly (Figure 3A).

Males present a significantly higher COVID-19 mortality risk [59,60]. The plasma concentration of inflammatory cytokines and chemokines such as IL-8 and IL-18 are increased in males infected with SARS-CoV-2 when compared to females. The exacerbated systemic inflammation in children and adolescents induces protective cross-reactive antibodies and these preexisting antibodies influences the severity of COVID-19 by SARS-CoV-2 infection, in contrast to elderly. It is also possible that both mechanisms, inflamming and preexisting antibodies influences the clinical outcome differences observed in children, adolescents and elderly (Figure 3A).

Outstanding Questions

The contributions of IFNs in viral infection responses is becoming clear. In SARS-CoV-2 infections, how can we restore the correct IFNs balances? What are the quantitative values for a proper clinical correction in the IFNs balances? What are the possible adjuvant therapies to be included for viral clearance with acceptable side effects in patients? How does TNFα affect IFNγ activities and vice-versa? Does TNFα interact with Type I or Type III IFNs in epithelial tissue proliferation and repair? Can the use of IFNs or influenza infection increase SARS-CoV-2 infections by the increase of its cellular receptor ACE2? Are these interplays occurring in the infections with the new strains of SARS-CoV-2?

Search Strategy

Data search and selection were identified through searches from PubMed with the following search terms: “COVID-19”, “SARS-CoV-2”, “Influenza”, “Interferons”, “Cytokine storms”, “immune response”. Only articles published in English between 2005 and 2021 were included.

Contributors

All the authors contributed in the discussion, writing, literature searches and revision of the manuscript. All the Figures were mentored and designed by PLH and MAA
Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors would like to thank the financial support of the Brazilian financial agencies Fapesp (Grant 2020/07040–1 to PLH), CNPq (Grant 505430/2019-0 to PLH) and Fundação Butantan as well as all the comments received from the reviewers. We also declare that the funders had no role in paper design, data collection, data analysis, interpretation and writing of the paper.

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