Interfering with SARS-CoV-2: are interferons friends or foes in COVID-19?

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Type I and type III interferons are among the most potent anti-viral cytokines produced by the immune system. The recent outbreak of SARS-CoV-2, which causes COVID-19, underscores the vital role of these cytokines in controlling the virus and dictating disease severity. Here we delineate the pathways that lead to interferon production in response to SARS-CoV-2 encounter, and elucidate how this virus hinders the production and action of these cytokines; we also highlight that these interferon families serve protective as well as detrimental roles in patients with COVID-19, and conclude that a better understanding of the time, dose, localization, and activity of specific members of the interferon families is imperative for designing more efficient therapeutic interventions against this disease.

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Introduction

Emergence of the novel SARS-CoV-2 virus at the end of 2019 has reshaped the medical and socioeconomical habits of our societies. While the accelerated introduction of new vaccine platforms based on the use of adenoviruses or RNA has successfully enabled viral spread to be contained in several countries, the limited availability of these vaccines and the logistic limitations linked to their storage at controlled temperatures, has exposed numerous regions of the world to uncontrolled surges of COVID-19. The wide spread of the virus is associated with introduction of new variants of concern that will further prolong the pandemic and its detrimental effects. Despite this, the new virus — to which we have limited, if any, pre-existing immunity — presents a unique opportunity to better understand the functioning of the human immune system [1], and knowledge derived from past and ongoing studies of SARS-CoV-2 has yielded unprecedented insight into unknown aspects of the immune response, and has identified potential new therapeutic targets and drugs that may be used not only against SARS-CoV-2, but also against viral infections in general, and/or against other immune-mediated pathologies.

COVID-19 is a pathology initiated by SARS-CoV-2, but the most severe cases of COVID-19 appear to be linked to an exaggerated and deregulated immune response. In severe COVID-19, the immune mediators that are produced to restrict viral spread also cause dysfunction of the lung, as well as of other tissues and organs. Unraveling the extent to which a specific immune mediator plays a key protective or detrimental role is probably one of the major challenges for the scientific community. We argue here that the timing and dosing of the production of various immune mediators, and the location where these mediators are produced, must be taken into consideration to effectively understand their roles, and to come up with better strategies for designing therapeutic interventions.

In this review, we frame COVID-19 in the broader context of immune-driven pathologies, and then focus on the two major families of IFNs — type I and type III IFNs — best known for their potent anti-viral properties [2,3]. Type I IFNs are mainly represented by several IFN-α's (13 in humans) as well as by IFN-β [3], while type III IFNs belong to the IL-10 family of cytokines and are represented by IFN-λ1-4 in humans (only IFN-λ2 and IFN-λ3 exist in mice) [4•,5•,6•]. These two families of IFNs signal via different receptors (the IFNAR and the IFNLR, respectively), but the signaling cascades initiated by type I and type III IFNs are very similar, and drive the transcription of a similar set of genes, termed the interferon-stimulated genes (ISGs). The major difference between these two families of IFNs is reflected in the pattern of expression of their receptors; while the IFNAR is expressed almost ubiquitously in the body, expression of the IFNLR is limited to epithelial cells and few immune cells. Thus, type III IFNs are believed to be gatekeepers of mucosal surfaces that efficiently restrict viral replication, and at the same time limit the inflammatory response at the mucosae [2]. Here we discuss the production and functions of these IFNs in the context of the anti-viral response, and also review what is known about their role in participating to the immune-mediated damage that characterizes severe COVID-19.

COVID-19 is an inflammatory disorder

A key feature of severe COVID-19 is an exuberant activation of the immune system, and severe forms of SARS-CoV-2-driven pathology are characterized by production of high levels of numerous pro-inflammatory cytokines and chemokines [1]. This inflammatory response favors the recruitment and activation of multiple immune cells to the lungs, and it also results in systemic inflammation [7,8]. The virus potentially infects multiple human cell types in a number of organismal locations [9,10], but the damage and dysfunction that occur in several tissues are mainly linked to secondary immune-mediated responses, rather than to the presence of the virus itself [11] or to the viral load [12]. The term 'cytokine storm' is still controversial [13,14], but severe COVID-19 is broadly recognized as an inflammatory disorder mediated by an uncontrolled immune response [14,15]. The inflammatory nature of this pathology is also reflected by the fact that the only effective pharmacological interventions for preventing or restraining the most severe cases involve the use of anti-inflammatory drugs. Except for Remdesivir (which is indicated for non-critical patients), the other drugs in current use are immunomodulatory agents [16–21].

The inflammatory nature of COVID-19 leads to interesting parallels with sepsis, one of the most studied and less curable inflammatory disorders. Sepsis is characterized by the simultaneous activation of pro-inflammatory and immune-suppressive events [22,23]. In particular, the unbalanced production of pro-inflammatory mediators that occurs in sepsis is accompanied by a failure to return to homeostasis; in other words, tissues and organs are unable to return to their initial functional state, and yet cannot adapt to a new one as a consequence of fluctuating environmental conditions driven by the infection or tissue injury. The 'failure of homeostasis' phase during sepsis is characterized by immunosuppression (both for immune as well as metabolic functions) and by persistent critical illness (PCI) [23]. Severe COVID-19 is characterized by increased cell death: the elevated levels of interferon (IFN)-γ and TNF that are observed in patients with severe disease induce a form of cell death called PANoptosis [23], which initiates a feed-back loop that sustains lymphopenia, tissue damage, and inflammation. Another key feature of the immunosuppressive phase of sepsis is decreased antigen presentation — this is also a hallmark of severe COVID-19, that is characterized by HLA-DR^{lo} circulating monocytes and dendritic cells [24–26]. In addition, the gene signatures of monocytes derived from patients with severe sepsis and from those with severe COVID-19 are strikingly similar [15]. In keeping with an immunosuppressive environment, adaptive immune responses are also altered in patients with severe COVID-19 (as recently reviewed in Ref. [27]) — this is illustrated by induction of BCL-6$^+$ Tfh cells being altered in patients who succumb to severe COVID-19 [28[•]], and

by the tight link between disease severity and delayed antibody production or CD8 T cell responses [12,29].

As observed in most immune dysfunctions, profound organismal and cellular metabolic changes are also found in individuals who are severely infected with SARS-CoV-2. By altering one-carbon and folate metabolism, the virus favors its own growth [30]. Loss of nutrient metabolites and lipids is common to patients with severe COVID-19 as well as other severe infections [31,32], while profound alterations in the levels of iron and iron transporters are associated with ferroptosis, and possibly with further increases in cell death and disseminated tissue damage in patients with severe COVID-19, as has been proposed recently [33]. At the same time, the metabolism of adaptive and innate immune cells is also changed: patients with COVID-19 exhibit an altered balance between respiration and glycolysis in their lymphocytes, and this change culminates in VDAC-dependent induced apoptosis [34]. Monocytes and neutrophils also display metabolic changes that are typically associated with immunosuppression [34]. Finally, post-acute sequelae of SARS-CoV-2 infection (PASC) (reviewed in Ref. [35]), also known as long COVID-19, may share several aspects with PCI, although the study of these sequelae is still in its infancy.

Besides the striking similarities between the failure of homeostasis phase in severe COVID-19 and sepsis, production of pro-inflammatory mediators also serves key functions in SARS-CoV-2-infected patients who are suffering from a severe pathology. As mentioned above, the major pharmacological treatments currently utilized to treat severe COVID-19 are aimed at decreasing cytokine and chemokine — driven inflammatory responses. The relevance of several inflammatory mediators involved in COVID-19 has been extensively analyzed [1,8,36–38]. In the rest of this review, we thus focus our attention mostly on the role of type I and type III IFNs during COVID-19.

Sensing of SARS-CoV-2, and induction and inhibition of IFNs *in vitro*

SARS-CoV-2 is a positive-sense single-stranded RNA (ssRNA$^+$) virus that forms double-stranded (ds)RNA intermediates during replication. Pattern recognition receptors (PRRs) that recognize RNA viruses are mainly represented by endosomal TLR7/8 and TLR3, and by the cytoplasmic RNA-sensing receptors MDA5 and RIG-I [39]. RIG-I and MDA5 recognize SARS-CoV-2 RNA as well as intermediates of replication of the virus inside infected cells [40–42], while other PRRs are involved in virus recognition by bystander and/or non-infected cells. Several C-type lectins (such as DC-SIGN) and Tweety family member 2 (TTYH2) bind SARS-CoV-2 spike protein, and induce pro-inflammatory responses in myeloid cells [43]. In keeping with recognition of SARS-CoV-2 by non-infected cells, TLR2 binds the SARS-CoV-2

envelope to induce inflammation, in the absence of internalization of the virus [44]. dsRNA that is formed during replication of a ssRNA virus may be released by dying infected cells, and is subsequently taken up by phagocytes and recognized via TLR3, as recently suggested for COVID-19 [2,45••]. Finally, the cGAS-STING pathway also recognizes SARS-CoV-2 and participates in triggering inflammation [46].

Although several PRRs recognize SARS-CoV-2, their effectiveness in mounting an immune response, and in particular in producing anti-viral IFNs, is challenged by numerous mechanisms that are initiated by the virus to inhibit the receptors from recognizing it, to prevent the immune response from being triggered, and/or to abrogate IFN production or signaling via numerous effector proteins, as reviewed elsewhere [36]. For example, multiple SARS-CoV-2 viral effectors disrupt cellular (but not viral) RNA splicing and translation, and also block the protein trafficking that would enable secretion of proteins as well as release of anti-viral mediators [47,48]. SARS-CoV-2 proteins also degrade host cell mRNA, and prevent the export of nuclear mRNA [49]. These are just a few among many of the strategies utilized by SARS-CoV-2 to support its own growth and prevent the production of IFNs, among other immune mediators. This strategy is particularly relevant for cells wherein the virus is actively replicating, and which are the first to respond to the virus.

SARS-CoV-2 is believed to effectively shut down the production of IFNs, and thereby favor its own spread from the upper to the lower airways, where it initiates the complex mechanisms that cause a severe pathology. However, recent findings have challenged this view. Epithelial cells in the human airways respond to viral challenge by producing type I IFNs [50], and alveolospheres that are infected with SARS-CoV-2 not only show signs of dysfunction (mirroring that seen in infected patients), but also produce type I and type III (but not type II) IFNs [51,52]. Whether production of IFNs under these experimental settings is driven directly by cells infected with the virus, or by bystander cells that sense the presence of viral or cellular inflammatory cues, remains to be determined. Also, human bronchial epithelial cells cultured at the air-liquid interphase can produce type I and type III IFNs when stimulated by either RIG-I or TLR3, but not in response to several other PRR ligands [45••]. Together, these findings suggest that epithelial cells that are directly infected, or that sense the presence of dsRNA derived from dying infected cells (via RIG-I or TLR3 respectively), may participate in the anti-viral response. In addition to the epithelial cells, other immune cells may also be involved in recognizing SARS-CoV-2: plasmacytoid dendritic cells (DCs) and conventional (c) DCs, also contribute to this process [45••,53••,54–56]. How IFNs produced by different immune and non-immune cells influence the restriction of viral replication *in vivo* remains to be addressed.

Another important unresolved issue concerns the relative contribution of different IFNs to restricting the virus. *In vitro* studies show that a set of specific ISGs is critical for controlling the replication of SARS-CoV-2 [57]; also that specific members of the IFN families, in particular IFN-λ1 and IFN-γ [58], or IFN-α5 [59], are efficient inhibitors of SARS-CoV-2 replication. Thus, a critical question is how the ability of distinct cell types to produce specific IFNs (in response to a variety of PRR stimulations [45••]) affects the induction of particular ISGs, and in turn the restriction of SARS-CoV-2.

Production of type I and type III IFNs in patients with COVID-19

Besides the capacity of SARS-CoV-2 to induce and antagonize IFN production in different cell types *in vitro*, a foremost concern during this pandemic has been to establish the role played by IFNs in SARS-CoV-2-infected patients. Given that type I and type III IFNs are among the most potent natural anti-viral mediators, the following questions need to be addressed: are IFNs produced in patients with COVID-19, is their localization and timing of production relevant for the development of SARS-CoV-2 infection, and do they exert a protective role against severe COVID-19?

An early study used RNA sequencing (RNAseq) to analyze post-mortem lung tissue from two patients who were severely affected with COVID-19, and concluded that pro-inflammatory cytokines and chemokines are potently induced in the lung as well as in the peripheral blood, while their ISG signature is reduced, compared to that in patients infected by other common respiratory viruses. Also, that type I and type III IFNs are absent in the peripheral blood of these COVID-19 patients [60••]. This paper was among the first to highlight the inflammatory nature of severe COVID-19, and to raise awareness about the involvement of the immune system in patients afflicted with severe SARS-CoV-2 infections. Another report analyzed data from 50 patients who had COVID-19 (pathology ranging from mild to critical) in terms of their capacity to produce type I IFNs. The authors measured gene transcripts and levels of protein, and confirmed that the IFN gene signature, and also the type I IFNs, were not induced in the peripheral blood of patients with severe and critical disease [61]. In contrast, mild-to-moderate cases of COVID-19 produced type I IFN and also showed an ISG signature [61]. These findings have been further verified by several groups, who used single cell and/or bulk transcriptomics, and in some cases also measured IFNs at the protein level [62–64].

Reports reported above have documented that IFNs or their corresponding signature are either absent or only transiently upregulated in patients with severe COVID-19. Other studies, instead, have reported a different trend for the production of IFNs in COVID-19 patients: longitudinal analyses of the peripheral blood of COVID-19 patients revealed that type I and type III IFNs, and also the ISGs, were induced, but only at late time points following infection [65••,66]. In keeping with the production of IFNs in COVID-19 patients, the ISG signature in tissues derived from the lungs of COVID-19 patients pointed to a potent upregulation, relative to that in patients with other bacterial or viral pneumonias [67•]. In particular, IFNs and/or ISGs were readily detected at the RNA level, when measured locally in inflamed areas of the lung or in areas where SARS-CoV-2 was also detected [11,68]. A potent induction of IFNs was also reported at the mRNA or protein levels in the bronchoalveolar lavage fluids of patients with severe COVID-19 [45••]. Not only was induced the transcription of type III and type I IFNs in these patients, but a unique protein IFN signature (comprising all three families of IFNs) was also found to be a hallmark of the severely infected patients compared to non-microbially infected patients, and also to patients suffering from other bacterial or viral acute respiratory distress syndrome (ARDS) [45••]. Of note, no or very limited correlation between the protein content of the IFNs [45••] as well as of the transcriptional signature [69] in the lungs compared to that in the blood of the same group of patients was found. Finally, a tight correlation was found between the production of type I and type III IFNs and/or the ISGs and the levels of SARS-CoV-2 in the upper airways of COVID-19 patients: as the viral load in the upper airways increased, so did the IFN signature [45••,70•,71,72]. These data indicate that the viral effectors (described above) that inhibit IFN production cannot efficiently prevent IFN induction when the virus burden increases, or that bystander cells can sense either viral or endogenous signals that drive IFN production in cells that are not infected with SARS-CoV-2.

Collectively, these studies highlight the complexity of IFN production during COVID-19 (Figure 1), and underscore how the timing of measurement, the choice of organs analyzed, as well as the diversity of the patient cohorts in terms of disease severity may impact this type of analyses. Several of these works also raise the possibility that IFNs, and the IFN-dependent gene signature, may drive detrimental roles during COVID-19, rather than protection.

Protective and detrimental roles of IFNs in COVID-19 patients

The finding that type I and type III IFNs are produced in COVID-19 patients raises the issue of whether they serve a protective or detrimental role. Given that these families
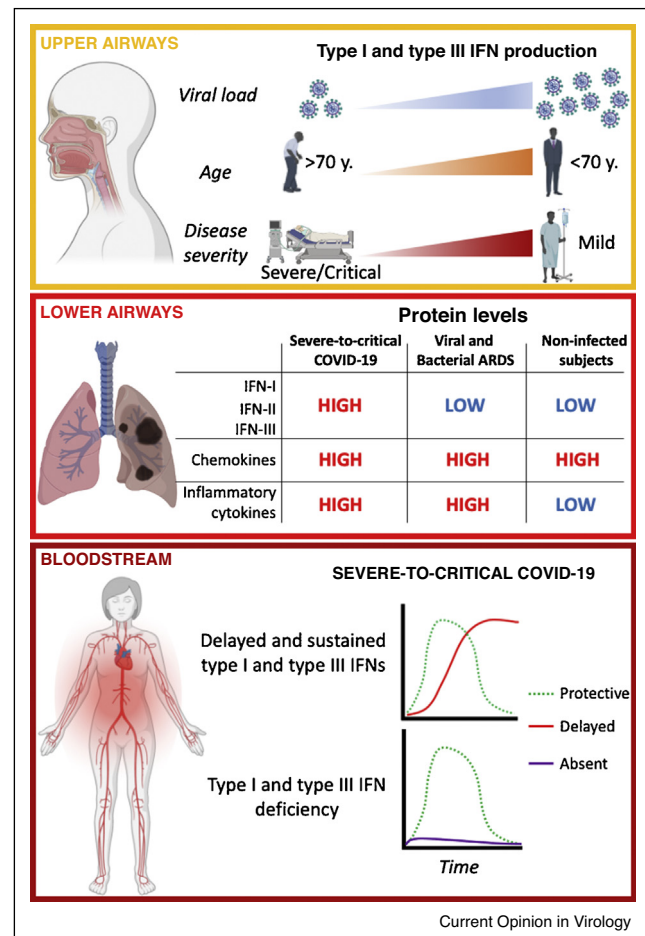
Type I and type III interferons as determinants of the severity of COVID-19. Type I and type III IFNs play key roles during COVID-19 development. In the upper airways, a potent production of type III, and to a lesser extent type I, IFNs is associated with increased viral loads, younger age and milder pathology. In the lower airways, high levels of type III (and type I) IFNs characterize the lung of severe-to-critical COVID-19 patients. In the blood, the absence of IFN production and/or responses, as well as a delayed and prolonged production of type I and type III IFNs has been associated with negative outcomes of COVID-19, while a transient and early production of IFNs has been associated with a mild disease.

of IFNs serve anti-viral roles, that IFNs were initially reported to be reduced in patients with severe COVID-19, and that SARS-CoV-2 reportedly has the capacity to inhibit IFN production and signaling, the general viewpoint in the field was that type I and type III IFNs are protective during COVID-19. In fact, an analysis of more than 1600 patients with COVID-19 uncovered genetic defects in TLR3, IRF-9, or IRF-7 that impair either the production or signaling downstream of type I or type III IFNs, and that these defects are associated with up to 3.5% of cases afflicted with severe disease [73••]. The same group also showed that up to 2.6% of females, and up to 12.5% of males with severe disease present auto-

antibodies directed against type I IFNs [74[••]]. More recently, TLR7-deficency has been also implicated in severe COVID 19 [88]. Additionally, autoantibodies against CD32 suppress ISG induction in patients with severe disease [64] and levels of gene expression of the *IFNAR2* (that encodes one of the two subunits of the receptor for type I IFNs) are also decreased [75]. A study of the broader landscape that pertains to autoantibodies elicited in COVID-19 patients concluded that autoantibodies directed against type I IFNs present in around 5% of patients but also that these patients bear autoantibodies directed against proteins involved in leukocyte function, activation and trafficking, type I and type III IFN responses, type II immunity, and the protein of the acute phase response [76[••]]. A principal component analysis revealed that autoantibodies against chemokines and cytokines can be used as significant predictors of the severity of COVID-19: in particular, type III IFNs were among the proteins targeted by the autoantibodies that drove the association with disease severity. The paper also showed that autoantibodies directed against type I IFNs dampen viral clearance, and that injection of anti-IFNAR antibodies in K18-ACE2 transgenic mice infected with SARS-CoV-2 induced more severe disease. Finally, in keeping with IFNs being protective against severe COVID-19, it was documented that a large proportion of patients with pre-existing autoantibodies against type I IFNs (due to loss-of-function variants in the *AIRE* gene) developed severe-to-critical COVID-19 [77]. Also, that autoantibodies directed against type I IFNs are present also in uninfected patients [89].

Production of IFNs or ISGs was analyzed locally in the upper airways of patients with COVID-19 in several reports [45[••],70[•],71,72]. Studies that utilized whole [71] or single cell [70[•]] RNAseq concluded that a potent induction of ISGs in the upper airways was associated with protection against SARS-CoV-2, but these works did not detect IFNs in their samples. In contrast, another study identified specific members of the type I and type III IFN families in the upper airways of a cohort of more than 150 subjects, and concluded that efficient induction of IFNs, especially of type III IFNs, occurs only in younger COVID-19 patients (who are less susceptible to severe COVID-19 [78]) and is found in individuals who are home-isolated with mild disease, rather than in those who are hospitalized, or in ICU [45[••]]. Intriguingly, patients with mild COVID-19 are primarily characterized by the production of IFN-λ1 and IFN-λ3 [45[••]]. Another recet study also confirmed the upregulation of IFNs in the upper aiways of patients with mild COVID-19 [90]. These data further support the important roles of IFNs in preventing severe and/or critical COVID-19, and expand this concept to the upper airways, suggesting that a major function of the IFNs is to prevent the spread of the virus from the upper to the lower airways. Nevertheless, recent studies question the global relevance of anti-

type I IFN autoantibody, as well as of genetic defects associated with IFN production and/or signaling, in driving severe COVID-19, and suggest that other factors exert equally important protective and/or detrimental functions [79,80].

This complex association between IFN production and COVID-19 severity was confirmed in patients with severe COVID-19, who exhibited an increased ISG signature in their blood [81], and in whom the elevated levels of type I and type III IFNs in the peripheral blood were correlated with negative outcomes of severe COVID-19 [65[••]] (Figure 1).

If and how potent IFN-mediated responses favor severe COVID-19 remains to be fully elucidated. One possibility is that the type I IFNs have a pro-inflammatory activity. This is supported by the increased IFN signature of peripheral monocytes in patients with severe COVID-19, compared to those with mild disease [81]. A non-exclusive alternative is that type I and, especially, type III IFNs play a detrimental role, as recently described in mouse models of RNA virus infections [53[••],82[•]]. These studies point to a role for IFN signaling in preventing the proliferation of lung epithelial cells and in facilitating their apoptosis; in turn, these events delay tissue repair, favor lung permeability and impair lung barrier functions. The findings are even more critical in light of the high levels of IFNs, particularly type I IFNs and IFN-λ2, detected in the lower airways of patients with severe COVID-19 [45[••]]. In keeping with data obtained in mouse models, these severe patients also present gene signatures associated with decreased proliferation and increased p53 activity [45[••]]. Also, it has been recently demonstrated that type I and type III IFNs dramatically increase expression of ACE2 and TMPRSS2 to boost viral entry in alveolar epithelial cells [83]. IFNs have been shown to upregulate only a truncated, non-funcitonal, form of ACE2 [91,92]. Nevertheless, these new data reveal the possibility that a combinantion of cytokines - comprehending IFNs - may favor viral entry, possibly unveiling another detrimental effect of these immune mediators in the lower airways of COVID-19 patients. It is, though, important to mention that studies focused on the activity of type III IFNs in the gut revealed a protective role for this group of IFNs on intestinal epithelial cells [84,85], as well as their capacity to reduce tissue damage by dampening neutrophils' functions [86[•]]. It is possible that either the nature of the agent that drives the inflammatory process, or the duration, for example, persistent incapacity to eliminate SARS-CoV-2 as opposed to transient tissue damage of the gut epithelial layer — drive different functions of IFNs. Overall, the apparently opposing roles played by type III IFNs in the gut and in the lung give a potent mandate to further analyze their biology and signaling activity.

In sum, these observations reveal a complex regulation of the type I and type III IFN families during the development of COVID-19. The timing of the response appears to be fundamental, with an early, transient IFN production being correlated with a milder pathology, as previously discussed [38]. The data discussed above add another layer of complexity linked not only to the timing, but also to the localization of the response, with efficient induction of IFNs in the upper airways being protective, while sustained production of IFNs in the lung or in the blood driving detrimental roles. The cell types that produce and/or respond to IFNs may also be a factor in this complex phenotype [45••], and an intriguing possibility is that only certain types of IFNs, and/or cells that respond to specific IFNs, initiate the transcriptional programs associated with protection against SARS-CoV-2, or favor detrimental outcomes of COVID-19.

Conclusions

The emergence of the new SARS-CoV-2 virus has enabled detailed insight into the immune response to a virus for which no previous immunity is broadly present in humans. This event highlights unique features of the host-pathogen response, with type I and type III IFNs playing complex and somewhat contrasting roles. The complexity of the response is evidenced by the difficulty of harnessing recombinant IFNs (namely, drugs that are widely available and are used to treat several pathologies) for use as anti-virals against SARS-CoV-2. In fact, studies that have utilized recombinant type I and type III IFNs report opposing effects, as reviewed elsewhere [87]. We posit that the dosing, route, and timing of administration, as well as the nature of the specific IFN utilized, will have profound impacts on the effectiveness of this type of treatment, and we contend that a better understanding of the complexity and specificity of action of each member of the IFN families, and of its targets, will help in the design of more efficient therapeutic interventions against COVID-19.

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Conflict of interest statement

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