INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China at the end of 2019, and it rapidly spread across the globe. On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a β-coronavirus with high sequence homology to bat coronaviruses (CoVs). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptor for viral entry into host cells. Human CoVs include two other highly pathogenic viruses, SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV. In this review, we describe the strategies by which SARS-CoV-2 evades IFN responses and the dysregulation of host IFN responses in COVID-19 patients. In addition, we discuss the therapeutic potential of type I and III IFNs in COVID-19.

Key Words: COVID-19, SARS-CoV-2, interferon, interferon-stimulated gene, therapeutics

Roles of Type I and III Interferons in COVID-19

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Coronavirus disease 2019 (COVID-19) is an ongoing global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Type I and III interferon (IFN) responses act as the first line of defense against viral infection and are activated by the recognition of viruses by infected cells and innate immune cells. Dysregulation of host IFN responses has been known to be associated with severe disease progression in COVID-19 patients. However, the reported results are controversial and the roles of IFN responses in COVID-19 need to be investigated further. In the absence of a highly efficacious antiviral drug, clinical studies have evaluated recombinant type I and III IFNs, as they have been successfully used for the treatment of infections caused by two other epidemic coronaviruses, SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV. In this review, we describe the strategies by which SARS-CoV-2 evades IFN responses and the dysregulation of host IFN responses in COVID-19 patients. In addition, we discuss the therapeutic potential of type I and III IFNs in COVID-19.

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known as IFN-λ1/IL-29, IFN-λ2/IL-28A, IFN-λ3/IL-28B, and IFN-λ4. IFN-λs bind to the IFNλ receptor, a heterodimeric receptor formed by IFNLR1/IL28Rα and IL10Rβ that is exclusively expressed on epithelial cells and certain types of myeloid cells.10 Due to this specific expression pattern, the antiviral effects of IFN-λs are especially prominent at epithelial barriers, such as those in the gastrointestinal, respiratory, and reproductive tracts.11-13

Although type I and III IFNs are genetically distinct and use different receptors, the downstream signaling pathways and the transcriptional responses activated by type I and III IFNs exhibit substantial overlap. The major difference is that type I IFN signaling results in a rapid, systemic induction and decline in ISG expression, whereas type III IFN signaling induces a sustained upregulation of ISGs in epithelial cells mediated by unphosphorylated STATs.14 In this manner, type III IFNs provide antiviral protection at epithelial surfaces as a frontline defense that confers less collateral damage than the more potent type I IFN response.15

As type I and III IFNs are involved in host protection against viruses,16-18 many viruses have developed mechanisms to evade and suppress the antiviral functions of IFNs and ISGs.19,20 In this review, we describe how host cells sense CoV infection and how SARS-CoV-2 evades the type I and III IFN responses. Furthermore, we describe the dysregulated IFN responses in COVID-19 patients and discuss the therapeutic potential of type I and III IFNs in COVID-19.

**Evasion of IFN Responses by SARS-CoV-2**

**Recognition of CoVs by the innate immune system**
The innate immune system detects viral pathogens by recognizing their pathogen-associated molecular patterns (PAMPs) through various PRRs. Viral PAMPs are distinct molecular patterns that do not exist in host cells, including viral single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA).21 Although our current understanding of the specific innate immune sensing of SARS-CoV-2 is limited, the virus-host interactions of SARS-CoV-2 are predicted to resemble those of other CoVs due to their shared sequence homology. Host cells rec--
During viral replication, viral RNA evades RLR recognition. Viral RNA is processed in ER-derived double membrane vesicles that are formed during viral replication. RIG-I-like receptors (RLRs) are widely expressed by the majority of cell types and localized in the cytosol, whereas TLRs are usually expressed by innate immune system cells and localized on the cell membrane and cellular compartments like endosomes. Downstream signaling of TLRs and RLRs upon ligand binding activates transcription factors, such as IRF3, to produce type I and III IFNs and nuclear factor-κB (NF-κB) to express pro-inflammatory cytokines, which together induce antiviral programs in host cells.

In the endosome, TLR3 detects dsRNA, while TLR7 and TLR8 detect ssRNA. CoVs are positive-sense ssRNA viruses that form dsRNA intermediates during their replication, which can be detected by TLR3 in the endosome, and by RIG-I, MDA5, and PKR in the cytosol. The ssRNA can also be detected by TLR7 or TLR8 in the endosome and potentially by RIG-I and PKR in the cytosol. The TLR located on the surface of innate immune cells, TLR4, recognizes viral glycoproteins, such as the respiratory syncytial virus fusion protein. Differences in the location of PAMP engagement can determine the type of IFN produced. For example, TLR4 engagement in the endosome results in the production of type I IFNs, whereas TLR4 signaling at the plasma membrane induces type III IFNs, which could explain the protective activity of type III IFNs at epithelial barriers that continually encounter PAMPs. TLR7 is crucial for sensing various CoVs, and is required for IFN-α production by pDCs in CoV infection. The cytosolic RLRs, RIG-I and MDA5, sense viral RNAs by detecting uncapped RNA bearing a 5’ triphosphate terminus, RNA with a non-methylated or incompletely methylated cap structure, and replicative intermediates consisting of dsRNA.

Evasion of innate immune sensing by SARS-CoV-2
CoVs, including SARS-CoV-1 and MERS-CoV, suppress PRR activation by either evading recognition or antagonizing PRR signaling (Fig. 1). To evade innate recognition, dsRNA is processed in ER-derived double membrane vesicles that are formed during viral replication. Viral RNA evades RLR recognition by generating a guanosine cap and methylation at the 5’ end by non-structural proteins (NSPs) 10, 13, 14, and 16. CoVs also evade dsRNA sensors, especially MDA5, by encoding an endoribonuclease, NSP15, which cleaves 5’ polyuridines from the negative-sense viral RNA formed during viral replication.

Recent studies have emphasized the possibility that SARS-CoV-2 is more efficient than other CoVs in inhibiting IFN signaling and activity. SARS-CoV-2 proteins have high amino acid sequence homology along with those of SARS-CoV-1, including NSP14, NSP15, NSP16, and N protein, suggesting that the evasion mechanisms of SARS-CoV-1 are likely preserved in SARS-CoV-2. In addition, NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6, and M protein inhibit virus-induced IFN-β production; and ORF6 inhibits type I IFN production and its downstream signaling. A SARS-CoV-2 protein interaction map obtained from the analysis of 26 SARS-CoV-2 proteins expressed in human cells identified host proteins that physically interact with SARS-CoV-2 proteins. SARS-CoV-1 ORF3b was found to inhibit the induction of type I IFNs by inhibiting IRF3. Even though SARS-CoV-2 ORF3b protein is shorter than SARS-CoV-1 ORF3b, it was recently found to inhibit IFN induction more efficiently. Moreover, a natural variant encoding a longer ORF3b reading frame exhibits enhanced suppression of IFN induction. In addition, SARS-CoV-2 ORF9b, similar to SARS-CoV-1 ORF9b, has been found to localize on mitochondria and suppress IFN responses through association with TOM70. Furthermore, SARS-CoV-2 NSP13 and NSP15 have been found to interact with TBK1 and the TBK1 activator ring finger protein 41 (RNF41/Nrdp1). SARS-CoV-2 NSP1 was also recently found to bind 40S and 80S ribosomes, shutting down capped mRNA translation and obstruction of the mRNA entry tunnel, thereby blocking RIG-I-dependent innate immune responses. This feature was previously demonstrated for NSP1 encoded by other CoVs, including SARS-CoV-1. When cells are stimulated by IFNs, SARS-CoV-2 N protein antagonizes IFN signaling by inhibiting phosphorylation of STAT1 and STAT2.

As described above, SARS-CoV-2 has diverse mechanisms for evading IFN responses. However, these IFN signaling evasion mechanisms are able to work only in SARS-CoV-2-infected cells in which viral proteins exist, but not in other non-infected innate immune cells. This could explain how the innate immune cells can participate in delayed but exacerbated IFN responses in COVID-19 patients.

DYSREGULATION OF IFN RESPONSES IN COVID-19

Impaired IFN responses in COVID-19
Impaired IFN responses have been reported in COVID-19 patients, particularly in patients with severe disease (Table 1). SARS-CoV-1 infection has been shown to induce the production of pro-inflammatory cytokines and chemokines but suppress the induction of IFNs. Accordingly, negligible amounts of IFN-β and IFN-λ have been detected in the sera of COVID-19 patients, whereas moderate levels of ISGs and strong expression of chemokines have been found consistently across in vitro, ex vivo, and in vivo models of SARS-CoV-2 infection. Another study has reported that patients with severe and critical COVID-19 exhibit a highly impaired type I IFN response, characterized by low levels of IFN-α and IFN-β and low levels of ISG expression. In addition, the majority of COVID-19 patients with acute respiratory failure have profound suppression of type I and II IFN responses compared to patients with acute influenza. The impaired IFN production in...
COVID-19 patients can be explained by pDC depletion, as pDCs are the main producers of type I IFNs. In severe cases of COVID-19, the number of pDCs is significantly decreased in the peripheral blood and bronchoalveolar lavage (BAL) fluid. 

Other studies have suggested that IFN induction may be delayed rather than completely impaired. Analysis of SARS-CoV-1-infected bronchial epithelial cells revealed that the production of IFNs is delayed compared to the production of pro-inflammatory cytokines. Furthermore, the induction of IFN-α, IFN-β, and ISGs in SARS-CoV-1- and MERS-CoV-infected cells is delayed compared to that in influenza A virus (IAV)-infected cells. SARS-CoV-1-infected mice with severe symptoms exhibit robust viral replication and delayed type 1 IFN

| Table 1. Summary of Published Studies Regarding IFN Production and ISG Response in COVID-19 Patients |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Cohort Specimen | ISG response | Production of IFN | Refs |
| 24 COVID-19, 24 healthy PBMC | Moderate ISG response, strong chemokine expression | Low IFN-I and IFN-III level | 38 |
| 50 COVID-19 (15 mild-to-moderate, 17 severe, 18 critical), 18 healthy PBMC | Impaired ISG response in severe and critical patients | No IFN-β low IFN-α production and activity in severe and critical patients | 39 |
| 8 COVID-19, 5 severe influenza, 4 healthy PBMC | Strong type I IFN response co-existing with TNF-IL-1β-driven inflammation in classical monocytes of severe patients | nd | 75 |
| 113 COVID-19 PBMC | nd | Increased IFN-α production in severe patients | 74 |
| 26 COVID-19 (critical) PBMC | Low ISG expression, ISG correlated with IFN-α2 measurement | Low or no IFN-α production, no IFN-β and IFN-λ production | 57 |
| 76 COVID-19, 69 healthy PBMC | Increased ISG expression in T cells and monocytes which correlated with IFN-α concentration in plasma | Low IFN-α production, lack of type I IFN gene expression | 56 |
| 8 COVID-19, 20 healthy BALF | Increased ISG expression and chemokine-dominant hypercytokinemia | nd | 72 |
| 7 COVID-19 (4 ARDS), 6 healthy PBMC | Positive correlation between ISG of CD14+ monocytes and age, and negative correlation with time from fever onset | nd | 60 |
| 10 COVID-19, 5 healthy BALF, naso-oropharyngeal swab | | Increased IFN-α, IFN-β, IFN-λ mRNA in BALF | 67 |
| 19 COVID-19, 5 healthy Nasopharyngeal/ pharyngeal swab | Overexpression of cytokine/chemokine genes in non-resident macrophages of the airway epithelium in critical patients | nd | 71 |
| 9 COVID-19 (3 moderate, 6 severe/critical), 4 healthy BALF | Type I IFN response mainly expressed by neutrophils and FCN+ classical monocytes | nd | 76 |
| 5 COVID-19 (4 moderate, 1 severe), 2 IAV, 3 healthy PBMC | Increased ISG expression, and severe patients show stronger response to IFN and virus infection | nd | 65 |
| 10 COVID-19, 5 healthy PBMC | Increased ISG expression in CD14++ inflammatory monocytes | nd | 66 |
| 16 COVID-19, 6 normal Post-mortem lung samples | Two distinct pattern: ISGhigh, high cytokine production, high viral loads, limited pulmonary damage /ISGlow, low viral loads, high infiltrating activated CD8+ T cells and macrophages | nd | 68 |
| 79 COVID-19 (35 ARDS), 26 influenza (7 ARDS), 15 healthy PBMC | Lower expression of IFN-α response genes compared to influenza | nd | 55 |

IFN, interferon; COVID-19, coronavirus disease 2019; ISG, IFN-stimulated genes; TNF, tumor necrosis factor; ARDS, acute respiratory distress syndrome; PBMC, peripheral blood mononuclear cell; BALF, bronchoalveolar lavage fluid.
signaling. Type I IFNs induce an influx of inflammatory monocytes/macrophages and vascular leakage, and the pathology is diminished in the absence of IFN signaling.83

**Enhanced IFN responses in severe COVID-19**

Paradoxically, elevated IFN production and ISG expression are correlated with worse disease outcomes in CoV infection, including COVID-19 (Table 1).40-47 Clinically well-described SARS patients with poor outcomes have high levels of IFN-α and ISG expression, which could be associated with atypical innate and adaptive immune responses.48 In addition, IFN-α production is significantly correlated with the severity of MERS-CoV, and no apparent IFN-α response has been detected in patients with mild symptoms.49

BAL fluid samples from COVID-19 patients exhibit increased transcriptional levels of IFNA2, IFNB1, IFNL2, and IFNL3,70 as well as robust innate immune responses with notable hypercytokinemia and increased expression of ISGs, particularly ISG15, RSAD2/viperin, IFIT , and IFITM family members.71 High levels of IFN-α levels in sera 5–10 days from symptom onset have been associated with the severity of COVID-19.72 In a longitudinal study, patients with severe COVID-19 exhibited increased IFN-α production over time, whereas patients with moderate COVID-19 had decreased IFN-α levels.73 Single-cell RNA sequencing (scRNA-seq) analysis of peripheral blood mononuclear cells of COVID-19 patients showed hyper-inflammatory signatures across all types of immune cells.74 Specifically, classical monocytes from severe patients exhibited a type I IFN response in combination with TNF/IL-1β-driven inflammation, whereas those from mild patients exhibited only features of TNF/IL-1β-driven inflammation, suggesting a pivotal role of the type I IFN response in exacerbating inflammation in the progression to severe COVID-19.74 Other scRNA-seq studies of peripheral blood mononuclear cells have observed heterogeneous ISG signatures in CD14+ monocytes, with higher ISG scores showing a positive correlation with patient’s age,59 and a broad type I IFN response genes expressed mainly by neutrophils and, to a lesser extent, by FCN1+ classical monocytes.75

The pro-inflammatory roles of IFNs have been well described in a mouse model of SARS-CoV-1, which demonstrated that delayed but considerable type I IFN responses in SARS-CoV-1-infected BALB/c mice trigger the accumulation of monocytes and macrophages as well as the production of pro-inflammatory cytokines, resulting in lethal pneumonia, vascular leakage, and insufficient T cell responses.49 Pro-inflammatory roles of type I IFNs have also been shown in human ACE2 expressing mice infected with SARS-CoV-2.76 Using Ifnar−/− mice or Ifng−−/− mice, this study proved that type I IFN responses are necessary for the recruitment of pro-inflammatory monocytes and macrophages to the infected lungs. In addition, type I IFNs have been found to reprogram the macrophage epigenome to promote inflammatory activation.77 TNF is a classical pro-inflammatory cytokine, but it also has a paradoxical anti-inflammatory function to limit inflammation-associated toxicity.78 This effect is mediated by tolerizing genes encoding inflammatory molecules, causing hyporesponsiveness to additional TLR signals in monocytes and macrophages.77 Type I IFNs were found to abolish the tolerizing effect of TNF and potentiate monocytes and macrophages responsive to additional TLR signals bypriming chromatin to prevent the silencing of target genes of NF-κB.77 Park, et al.71 identified a gene module that was previously unresponsive to TLR signals due to TNF-induced tolerance but became responsive to TLR signals with type I IFNs pretreatment. This gene module was found to be significantly upregulated in the transcriptome of classical monocytes from patients with severe COVID-19, indicating a feedforward mechanism of type I IFN-induced hyperinflammation in severe COVID-19 cases.74 These results demonstrate that IFN responses are not impaired in COVID-19 patients and highlight their possible role in exacerbating inflammation, particularly in cases of severe COVID-19.

Recent studies have shown that SARS-CoV-2 receptor ACE2 in human airway epithelial cells is an ISG upregulated by type I and type II IFNs.79-81 These studies imply that exacerbated IFN responses could contribute to the cellular entry of SARS-CoV-2 and expand its cellular tropism, thereby promoting SARS-CoV-2 replication. Nevertheless, the antiviral action of IFNs against SARS-CoV-2 was shown to counterbalance the pro-viral effects of IFN-induced ACE2 upregulation.82

**THERAPEUTIC POTENTIAL OF IFNS IN COVID-19**

**Therapeutic potential of type I IFNs in COVID-19**

Numerous in vitro and in vivo studies have demonstrated the therapeutic efficacy of type I IFNs in SARS and MERS.83 Treatment with IFNs in cell culture and organoids has been shown to efficiently inhibit the replication of CoVs, including SARS-CoV-1, SARS-CoV-2, and MERS-CoV.40-41,84-88 Recent in vitro studies have highlighted that SARS-CoV-2 is highly sensitive to both IFN-α and IFN-β.40,41 In these studies, viral titers were remarkably reduced when IFN-α and IFN-β was administered prior to infection and reduced to a lesser extent when treatment was administered after infection, indicating that type I IFNs may be effective as either prophylactic or early treatment for COVID-19 patients. In China, guidelines for the treatment of COVID-19 recommend vapor inhalation of IFN-α twice a day in conjunction with ribavirin administration,89 which offers the advantage of delivering IFN-α specifically to the respiratory tract.

Several clinical trials have been registered to evaluate the efficacy of type I IFNs as a single or combination therapy for COVID-19 (Table 2). The multicenter, adaptive, randomized, open clinical trial DisCoVeRy is currently evaluating the effi-
Therapeutic potential of type III IFNs in COVID-19

Type III IFNs also trigger signals through the JAK-STAT pathway, inducing the upregulation of a pane of ISGs that substantially overlap with those induced by type I IFNs but demonstrate different context-specific functions. For example, IFN-λs are the predominant IFNs produced in the early phase of viral infection, as shown in IAV infection. IFN-λs act on IFN receptors, which are preferentially expressed by epithelial cells to control viral replication without causing hyper-inflammation. There is growing evidence that IFN-λs provide an important first line of defense against viral infection in the respiratory and gastrointestinal tracts. In mice, IFN-λs have been shown to protect respiratory epithelial cells from infection by respiratory viruses, including SARS-CoV-1. A recent study using human colon-derived cell lines and primary non-transformed human colon organoids revealed that SARS-CoV-2 infection can be controlled by both type I and III IFNs, although type III IFNs are more efficient at controlling viral replication. Furthermore, in a newly developed mouse model of SARS-CoV-2 infection, both prophylactic and therapeutic administration of pegylated IFN-λ1a diminished viral replication. However, recent studies have demonstrated that IFN-λs produced by lung dendritic cells in response to viral RNA lead to barrier damage, causing susceptibility to lethal bacterial superinfections. In addition, prolonged IFN-λ responses cause p53 activation, which reduces epithelial proliferation.

Table 2. Ongoing Clinical Trials Evaluating Efficacy of IFNs in COVID-19

| Phase | IFN | Form | Drug combination | Status | NCT number |
|-------|-----|------|------------------|--------|------------|
| 4     | IFN-β-1a | Recombinant | Hydroxychloroquine, lopinavir/ritonavir | Enrolling by invitation | NCT04350671 |
| 3     | IFN-α-1b | Recombinant | Thymosine alpha 1 | Recruiting | NCT04320238 |
| 3     | IFN-β-1a | Recombinant | Remdesivir, lopinavir/ritonavir, hydroxychloroquine | Recruiting | NCT04315948 |
| 3     | IFN-β-1a | Pegylated | Remdesivir | Recruiting | NCT04552379 |
| 3     | IFN-β-1a | Recombinant | Not recruiting yet | Recruiting | NCT04647669 |
| 3     | IFN-β-1a | Recombinant | Active, not recruiting yet | Recruiting | NCT04924757 |
| 3     | IFN-β | Recombinant | Recruiting | Recruiting | NCT04324463 |
| 2     | IFN-α-2b | Pegylated | Recruiting | Recruiting | NCT04480138 |
| 2     | IFN-β-1a | Recombinant | Not recruiting yet | Recruiting | NCT04449380 |
| 2     | IFN-β-1a (inhalation) | Recombinant | Recruiting | Recruiting | NCT04385095 |
| 2     | IFN-β-1a, IFN-β-1b | Recombinant | Hydroxychloroquine, lopinavir/ritonavir | Completed (April 27, 2020) | NCT04343768 |
| 2     | IFN-β-1b | Recombinant | Clofazimine | Recruiting | NCT04465695 |
| 2     | IFN-β-1b | Recombinant | Hydroxychloroquine | Completed (July 7, 2020) | NCT04350281 |
| 2     | IFN-β-1b | Recombinant | Ribavirin | Recruiting | NCT04494399 |
| 2     | IFN-β-1b | Recombinant | Lopinavir/ritonavir, ribavirin | Completed (March 31, 2020) | NCT04276688 |
| 2     | IFN-β-1b | Recombinant | Lopinavir/ritonavir | Not recruiting yet | NCT04521400 |
| 2     | IFN-β-1b | Recombinant | Remdesivir | Recruiting | NCT04330690 |
| 2     | IFN-β-1b | Recombinant | Remdesivir | Recruiting | NCT04647695 |
| 2     | IFN-β-1b (inhalation) | Recombinant | Recruiting | Recruiting | NCT04469491 |
| 2     | IFN-λ | Pegylated | Recruiting | Recruiting | NCT04345259 |
| 2     | IFN-λ | Pegylated | Recruiting | Recruiting | NCT04344600 |
| 2     | IFN-λ | Pegylated | Not recruiting yet | Recruiting | NCT04388709 |
| 2     | IFN-λ | Pegylated | Recruiting | Recruiting | NCT04534673 |
| 2     | IFN-λ | Pegylated | Enrolling by invitation | Recruiting | NCT04343975 |
| 1,2   | IFN-α-2b | Recombinant | Rintatolimod | Recruiting | NCT043756518 |
| 1     | IFN-α | Recombinant | Not recruiting yet | Recruiting | NCT04293887 |

IFN, interferon; COVID-19, coronavirus disease 2019.
and differentiation, increasing susceptibility to bacterial superinfections and their severity. Therefore, although the therapeutic potential of type III IFNs is promising, the clinical safety of type III IFNs in COVID-19 patients still needs thorough investigation. Currently, four clinical trials (NCT04343976, NCT04354259, NCT04386709, and NCT04344600) using pegylated IFN-λs are ongoing, all of them currently in phase 2 (Table 2).

CONCLUDING REMARKS

Type I and III IFNs are key players in the control of viral replication, but their roles in hyper-inflammation need to be further elucidated. Contradictory results regarding impaired or enhanced IFN responses in severe COVID-19 patients may be explained by differences in the definition of disease severity, sampling time points, and/or type of experimental readout (e.g., IFN itself or cellular responses to IFNs) among studies. Although there are some discrepancies in the roles of IFNs in COVID-19, recent clinical trials conducted with type I and III IFNs have shown promising results when treated in the early phase. A retrospective cohort study of 446 COVID-19 patients revealed that early administration of IFN-α2b is associated with reduced in-hospital days, whereas late IFN therapy in the later phase. A retrospective cohort study of 446 COVID-19 patients revealed that early administration of IFN-α2b is associated with reduced in-hospital days, whereas late IFN therapy increases mortality and delayed recovery. Other in vitro and in vivo studies support prophylactic treatment with IFNs as an ideal option. Therefore, in order to use type I or III IFNs as therapeutics for COVID-19 patients with minimal side effects, early treatment or prophylactic treatment before symptom onset would be optimal. Nevertheless, recent studies suggest that caution is needed when using IFN therapies, as prolonged IFN responses may cause lung epithelial barrier damage and lead to susceptibility to lethal bacterial superinfections.

Nevertheless, further clinical studies are needed to determine the efficacy and safety of recombinant type I and III IFNs for the treatment of patients with COVID-19.

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