viruses

MDPI

Review

Dysregulated Interferon Response Underlying Severe COVID-19

LeAnn Lopez[1,†], Peter C. Sang[1,†], Yun Tian[1,†] and Yongming Sang[1,*]

[1] Department of Agricultural and Environmental Sciences, College of Agriculture, Tennessee State University, 3500 John A. Merritt Boulevard, Nashville, TN 37209, USA;

[†] These authors contribute equivalently

* Correspondence: ysang@tnstate.edu; Tel.: 615-963-5183

Received: date; Accepted: date; Published: date

Abstract: Innate immune interferons (IFNs) including type I and III IFNs constitute critical antiviral mechanisms. Recent studies reveal that IFN dysregulation is key to determine COVID-19 pathogenesis. Effective IFN stimulation or prophylactic administration of IFNs at the early stage prior to severe COVID-19 may elicit an autonomous antiviral state, restrict the virus infection and prevent COVID-19 progression. Inborn genetic flaws and autoreactive antibodies that blocking IFN response have been significantly associated with about 14% patients with life-threatening COVID-19 pneumonia. In most severe COVID-19 patients without genetic errors in IFN-relevant gene loci, IFN dysregulation is progressively worsen and associated with the situation of proinflammation and immunopathy that prone to autoimmunity. In addition, the high correlation of severe COVID-19 with seniority, males and individuals with pre-existing comorbidities, will be plausibly explained by coincidence of IFN dysfunction in these situations. Collectively, current studies call for a better understanding of the IFN response regarding the spatiotemporal determination and subtype-specificity against SARS-CoV-2 infections, which are warranted to devise IFN-related prophylactics and therapies.

Keywords: COVID-19; Interferons; Interferon signaling; SARS-CoV2; Immunopathy

1. Diverted type I interferon (IFN) response associated with hyper-inflammation

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which causes the current pandemic of new coronavirus disease 2019 (COVID-19), shows an evolutionary success to adapt its infectivity and contagiousness to efficiently spread in human societies [1-6]. The prognosis of SARS-CoV2-infected patients is very broad, with a vast majority of people (50-80% based different research scenarios, CDC) only have mild symptoms like common cold or asymptomatic [7]; however, still the other significant numbers (averagely 20-50% based on different ethnicity and pre-medical conditions) may progress into severe respiratory and systemic syndromes needed immediate hospitalization and critical care [8-12]. The case fatality rate of COVID-19 ranges at 1.7-13.0% in different countries [7]. Except the pathogenic impact of viral infection, major pathologies underlying severe COVID-19 come from the dysregulation of vast immune factors at both the cellular and molecular levels. For example, severe COVID-19 patients display macrophage overreaction (also known as macrophage activation syndrome (MAS)) and lymphopenias of effective lymphocytes including neutrophils, CD4 T cells, and natural killer (NK) cells [13-15]. At the molecular level, hyper-regulation of proinflammatory mediators (including IL-6, TNFα, S100A8/9 and C-reactive protein), significant decrease of human leukocyte antigen D related (HLA-DR) gene expression in CD14 monocytes, and dysregulated antiviral interferon (IFN) response, have been reported in COVID-19 patients with critical illness [13-15]. In this review, we focus on the determinant role of dysfunctional IFN response underlying the progression of severe COVID-19. Interferon (IFN) system comprises a series of antiviral IFN cytokines, classified as type I, II and III based on their distinct molecular signatures and recognition

receptors in cells to induce hundreds for IFN-stimulated effector genes (ISGs) exerting various antiviral and other immunomodulatory functions (Figure 1) [16-18]. The IFN molecules of three IFN types are further designated into subtypes, which include the single IFN-γ for type II and IFN-λ1-4 for type III such as in humans. There are multiple subtypes of type I IFNs, which include general subtypes of IFN-α and IFN-β produced by most cells, and more cell-specific subtypes including IFN-ε (reproductive tract), IFN-κ (keratinocytes), IFN-ω (leukocytes/epithelial cells), and species-specific subtypes of IFN-δ (pigs), IFN-τ (cattle) and IFN-ξ (mice) [16-18].

Studies using transcriptomic analysis in SAR-CoV2-infected human bronchial cells or IFN assays in clinical plasma samples, demonstrated a distinct immune-reaction phenotype in symptomatic COVID-19 patients, being a highly impaired interferon (IFN) response [19,20]. The impaired type I IFN response was characterized by decreased IFN-α/β expression in both SARS-CoV2 infected human bronchial cells and circulating mononuclear blood cells, which was diagnosed together with a persistent viremia and an exacerbated inflammatory response upon reactions to increased pro-inflammatory mediators including tumor necrosis factor–α (TNF-α) and interleukin (IL)-6 [19,20]. Together with other previously in vitro studies, these data suggest that SARS-CoV2 bears similar antagonistic mechanisms as other severe human coronaviruses (i.e. SARS and MERS) to interfere with the host IFN signaling, especially the production of type I IFNs (Figure 1) [21,22]. In contrast, other studies by Lee et al. (2020) and Lucas et al. (2020) detected that patients with severe COVID-19 had a sustained type I IFN response and consistent proinflammatory response in the blood of patients subjected to severe COVID-19 [23,24]. Contradictory results about type I IFN responses in COVID19 patients may come from the disparity of criteria to define disease severity and different sampling times during the disease progression [25]. In addition, using large cohorts of COVID-19 patients in European countries, recent genome-wide associated studies (GWAS) have significantly associated several critical genetic loci with severe COVID-19, which contain genetic regions spanning multiple genes that are centered in both chemokine and IFN signaling [26,27]. All these studies highlight the potential role of IFN signaling in determining the host susceptibility to SARS-CoV2 infection and the progression of severe COVID-19 [19-27].

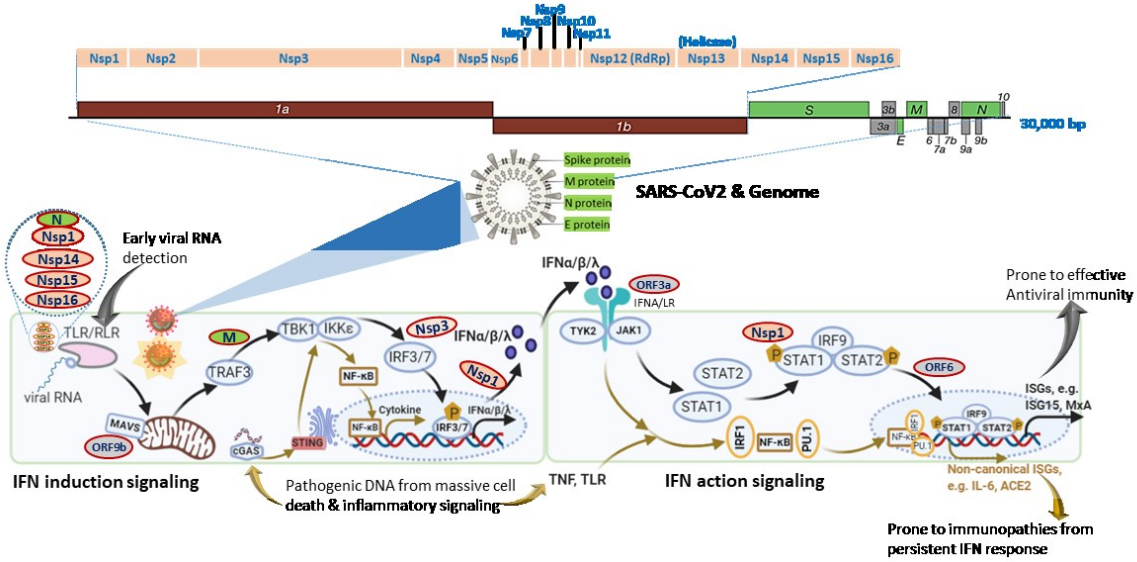

Figure 1: SARS-CoV2 genomic structure and analogical antagonism to interferon (IFN) signaling. Analogical to typical human β-coronaviruses, SARS-CoV2 genome contains ORF1a/1b encoding a polyprotein, which is proteolytically processed into non-structural protein (Nsp) 1–16 (top schematic). Structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins are diagramed to depict the genome and viron structures (middle). Other accessory proteins encoded at the 3′ end of the viral genome comprise ORF3a, 3b, 6, 7a, 7b, 8, 9a, 9b, and 10 (colored in grey). Bottom panel depicts SARS-CoV-2 proteins (colored ovals with red outlines) that

interfere with either IFN induction or action pathways, and are posited next to their known or hypothetic targets/steps in the IFN signaling. SARS-CoV2 seems evolving multiple antagonistic mechanisms against the host IFN signaling, and especially those on early IFN induction signaling. Note, cellular IFN induction may go with either a MAVS- or a STING-dependent pathways that respond to cytosolic pathogenic RNA or DNA molecular patterns, respectively. Similarly, IFN action signaling may lead through a canonical ISGs induction with limited pro-inflammation, or crosstalk with inflammatory signaling from TNF and TLR to increase the expression of non-canonical ISGs accompanying a proinfalmmatory and autoimmune ambient through epigenetic regulation. The canonical IFN signaling flow, which acts generally at early stage of SARS-CoV2 infection for primarily restricting viral infection, is depicted using black arrows; and brown arrows for the non-canonical IFN signaling flow activated at later stage in severe COVID-19, which is highly associated with pro-inflammation and immunopathies. Abbreviations: cGAS, cyclic GMP–AMP synthase; IFNA/LR, interferon alpha/beta OR lambda receptor; IKKε, IκB kinase-ε; IRF, IFN regulatory factor; ISG, IFN-stimulated gene; JAK, Janus kinase; MAVS, mitochondrial antiviral signaling protein; ORF, open reading frame; P, phosphate; TLR/RLR, Toll-like receptor or retinoic acid-inducible gene 1-like receptors; SARS-CoV, severe acute respiratory syndrome coronavirus; STAT, signal transducer and activator of transcription; STING, signaling effector stimulator of interferon gene; TBK1, TANK-binding kinase 1; TRAF3, tumor necrosis factor receptor-associated factor 3; TYK2, tyrosine kinase 2.

Interferon signaling, for either IFN induction or action, is not a linear cascade but an interacting network dynamically adapting to alternative and crosstalk with other cytokine signaling pathways [16-18, 25,27]. For IFN induction signaling during a RNA-virus infection as in COVID-19, the typical pathway is triggered by viral RNA through membrane-bound or cytoplasmic receptors (TLRs or RLR as in Figure 1), and culminated at IFN-regulatory factor (IRF)-3/7 activation and IFN expression. Alternatively, animal cells are also capable of inducing IFN expression through cellular receptor like cyclic GMP-AMP synthase (cGAS) to detect pathogenic DNA (pDNA) motifs from bacteria, viruses and dead cells, and to activate a stimulator of IFN genes (STING)-dependent pathway for IFN and inflammatory cytokine production (Figure 1, bottom-left panel). Similarly for IFN action signaling, the canonical IFN signaling is through engagement of membrane-bound IFN receptor (Figure 1, IFNA/LR for type I and III IFNs, respectively) and activation of STAT1/2 and ISGF3 transcription factors leading to robust expression of hundreds of classical IFN-stimulated genes (ISGs, such as ISG15, MxA, IFITM etc.), which exert antiviral role to restrict viral replication and spreading [16-18]. Alternatively, IFN signaling may divert to or synergize with TLR-mediated or cytokines (mainly TNF) signaling pathways to epigenetically promote the expression a group of recently characterized non-canonical ISGs (non-ISGs) [18,28,29]. Two newly characterized non-canonical ISGs are inflammatory cytokine IL-6 and angiotensin-converting enzyme 2 (ACE2), a key component in renin-angiotensin-aldosterone system (RAAS) and adopted by SARS-CoV2 as a primary cellular receptor for infection [30-32]. For a RNA-virus infection like in COVID-19, the canonical IFN induction and action signaling is plausibly activated early to induce IFN and ISG production due to cell perceiving the presence of viral RNA in infected cells. The non-canonical IFN signaling, for that responding to pDNA through cGAS-STING and non-canonical ISG stimulation via IFN-TNF epigenetic coordination might occur at the latter stage accompanying massive cell death from pyroptosis (a highly inflammatory form of programmed cell death in infected cells) and NETosis (an immunologically regulated form of neutrophil cell death) as seen in severe COVID19 cases [16-18,33-38]. In addition to induction of IFNs/ISGs, the canonical and especially non-canonical IFN signaling pathway also lead to the production of inflammatory cytokines, which is further exacerbated by the virus suppression of ACE2 activity to develop into a cytokine release syndrome (CRS) or cytokine storm [30,31,34-38]. We propose that the integration of both canonical and non-canonical IFN signaling sufficiently addresses the contradictory observations from different studies as discussed previously [19-25]. It explains that: (1) the weak IFN response is due to SARS-CoV2-suppression on the canonical IFN signaling mainly triggered by viral RNA species, which signifies the early stage of the disease prior to severe progression [19-21]; and (2) the robust IFN/ISG observations in severe COVID-19 cases accumulate consequential activation of non-canonical IFN signaling through both cGAS-STING for IFN production and IFN-TNF epigenetic regulation for ISG expression [23,24,33-

38], which mostly happen at the late stage of the severe COVID-19 or patients experienced complication of progressive pneumonia and multi-organ damage [23,24]. To support this proposal, most known IFN antagonistic mechanisms of SARS-like coronavirus evolve to target on major components of IFN canonical signaling, especially for IFN induction (Figure 1) [21]. Intensively, a study by Christopher et al. (2020) indicates that the IFN suppression of SARS-CoV2 (probably through NSP3 on IRF3) effectively curates inflammatory responses through cGAS-STING pathway, which correlates to immunopathies from IFN dysregulation as worsened in severe COVID-19 [37-39].

2. Immunopathological effect of dysregulated IFN responses

The suppression of IFN response, especially IFN production at the early stage of COVID-19 progression diminishes the host capacity to restrict (thus benefits) the virus spreading [19,20,40]. Notably, IFN system like all other immune mechanisms can be a double-edged sword to cause immunopathies given it is not activated appropriately in a right time or intensity [41-43]. As in COVID-19, both the early stage of type I IFN deficiency and the late stage of IFN persistence could be a hallmark of severe COVID-19 [19-24]. As well studied in the cases of major autoimmune diseases and chronic viral infections, type I IFNs (IFN-α and IFN-β) are widely associated with immunopathology [33,40-43]. In contrast, type III IFN (IFN-λ) responses are restrictively mucosa-specific and exert antiviral defense with less damaging from proinflammatory responses [17,43]. Accordingly, IFN-λ has been thought to have therapeutic advantages in COVID-19 [43]. However, updated studies in COVID-19 complicate the prophylactic promise of type III IFN-based clinical trials. Broggi et al. determined the subtype-dependent stimulation of type I and type III IFNs in the upper airway (naso-oropharyngeal swabs) and lung (BALF) samples, and their correlation to COVID-19 patient morbidity [44]. Data showed that the virus-positive BALF samples from the severe COVID-19 patients in ICUs contained significant higher human IFN-α/β and type III IFN-λ2/3 but not IFN-λ1 compared with either the virus-positive or –negative swab samples [45]. Further data from in vivo mouse models indicates that the inductive expression of IFN-α/β and IFN-λ2/3 by the lung immune cells (primarily dendritic cells) causes damage to the lung epithelium, which hampers lung repair and increases susceptibility to lethal bacterial coinfections [44-46]. Indeed, a meta-analysis evaluated 4.3-9.5% of COVID-19 patients with bacterial infection, which was more common in severe patients (8.1%) [47]; so were incidences of co-infection from other microbes including fungi and other viruses in critically ill COVID-19 patients, who suffer dysfunctional IFN and other immune reaction [48]. As mammalian IFN-α and IFN-λ2/3 subtypes evolve more inductive and antiviral activity than the epithelial-specific IFN subtypes (such as IFN-β and IFN-λ1) [49,50], robust reaction of inflammatory IFN responses via recruited immune cells in the lung certainly deteriorate the pulmonary homeostasis maintained by the epithelial IFN subtypes, which is more constitutively expressed by pneumocytes prior to immunopathic IFN responses in severe COVID-19. Therefore, more subtype-specific examination of the immunomodulatory and antiviral roles of both type I and type III IFNs in SARS-CoV2 infection is imperative for IFN-based prophylactic development [25].

3. Evidence from life-threatening COVID-19 cases with inborn IFN deficiency

By genetic screening of 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infections, Zhang et al., (2020) detected an enrichment in functional deficiency of 13 human gene loci that are known to govern TLR3- and IRF7-mediated antiviral IFN induction signaling in the severe COVID-19 patients [51]. These inborn errors in IFN induction ascribed to 23 patients (3.5%), who experienced life-threatening COVID-19 and aged 17 to 77 years. Despite a small proportion, the correlation indicate a group of genetic extremity (compared with progressive IFN suppression by the virus and potential comorbidity conditions) in IFN deficiencies that underlies life-threatening COVID-19 patients without prior severe infection [51]. Another study by Bastard et al (2020) revealed an autoimmune blocking on IFN action signaling [52]. In this case, they detected 101 of 987 (10.2%) patients with life-threatening COVID-19 pneumonia had auto-antibodies (auto-Abs), which were capable of binding and functionally blocking out almost all

subtypes of type I IFNs, particularly of IFN-α, IFN-ω, and both IFN-α/ω subtypes, in further antiviral regulation [52]. In a few cases, the auto-antibodies was also detected against the tissue-specific type I IFN subtypes including IFN-ε and IFN-κ typically expressed in the reproductive tract and skin keratinocytes, respectively [53,54]. In comparison, these auto-Abs were rarely found in the control cohort (663 individuals) who were SARS-CoV2-positive but asymptomatic or with mild signs [52]. Comparably, auto-Abs against type I IFNs were previously reported in patients subjected to IFN therapies and of systemic lupus erythematosus [55,56], and detected in almost all patients with autoimmune polyendocrinopathy syndrome type I (APS-1) [52,57]. In addition, 95% of the patients with the IFN auto-Abs were male, which may at least partially explain why men face higher risk of severe COVID-19 and resulted higher risk of mortality [10,11,52]. Collectively, evidence from both inborn deficiency and auto-immune blocking of IFN function elegantly demonstrate IFN signaling is a critical determinant of severe COVID-19 progression [51,52].

4. Category of IFN dysregulation underlying severe COVID-19 development

Figure 2 recaps our understanding about the dynamic interaction of the host IFN system to SARS-CoV2 infection and the progression of COVID-19 into a severe status. The majority of healthy individuals, who are capable of mounting effective IFN responses during the early phase of the viral infection, will be recovered naturally or without intensive medical care to escape from the worse progression [58-60]. However, for another proportion of patients, who have a pre-existing comorbidity or concur a chronic inflammatory condition, their IFN response will be swayed to an immunopathic situation to exacerbate the pneumonia in a severe COVID-19 development [61-63]. Dysregulation of IFNs and other immune factors have been associated with aging, sex difference, and pre-existing medical conditions, which have been clinically associated with a higher risk of severe COVID-19 [10-12,61-63]. Studies showed that both blood and lung dendritic cells (DCs), as a group of major IFN producers, whose capacity in IFN production is severely impaired in aged individuals when compared to juveniles. On the contrary, blood DCs from aged people secreted higher basal levels of proinflammatory cytokines/chemokines including IL-6, TNF-α, CXCL-8, CXCL-10 [64,65]. Together with other aging-associated lympocytic abnormalities [66], this IFN and inflammatory dysregulation in DC response in aged individuals may invoke lung inflammation, impair antiviral resistance and exaggerate major clinical signs as exacerbated in severe COVID-19 [8-12]. For the sex difference of IFN response, studies have demonstrated that plasmacytoid DCs (pDC) from healthy females are more potent to produce type I IFNs via TLR7-mediated signaling than the pDCs from males [67,68]. Plasmacytoid DCs serve as natural IFN producers and efficient sentinels in orchestrating antiviral immunity. This finding implicates an inferior status of males in the early antiviral IFN induction, a suitable stage for most IFN-based clinical trials having positive effect [25]. As for most preexisting medical conditions, including cardiovascular diseases, hypertension, obesity, and diabetes mellitus that increase the risk of severe COVID-19 [61,63], many studies have unraveled the progressive incidence of IFN insensitivity and chronic inflammation and have been reviewed elsewhere [40-42,69-71]. In addition, pathological consequence from persistent IFN and proinflammatory response as well as remarkable presence of auto-Abs represent typical pathological mechanisms underlying most autoimmune diseases including diabetes, multiple sclerosis and systemic lupus erythematosus (SLE) [40-42,69-71]. The dysregulation of IFN and other immune factors in the COVID-19 patients with pre-existing comorbidities, could be further complicated by the virus attacking on endothelial cells to cause vasculitis, aneurysms and coagulopathy as well as tissue damage in the kidney, heart and even brain [72-75]. The dysregulation of IFN response can be progressively resulted from the viral antagonism and virulence during viral replication (Figure 1). Furthermore, the preexisting comorbidities, gender and age inclination, and particularly exacerbated hyperinflammation associated with the IFN immunopathies and rigorous viral infection, will undermine the distinctness of immune and pathological responses and lead to a life-threatening situation or death [10-12,61-63]. The inborn genetic and autoimmune deficiency of IFN response have been shown in about 14% of the examined life-threatening COVID-19 patients [51,52], who may experience sudden consequence even without a severe progression thus, further associate the

dysfunction of IFN response with severe and life-threatening COVID-19 [51,52]. Hence, the prophylactic or therapeutic effect of IFN trial regimens should be carefully designed based on the temporal characteristics and subtype-specificity of IFN responses during SARS-CoV2 infection and the disease progression [25,49,50,53,54,76].

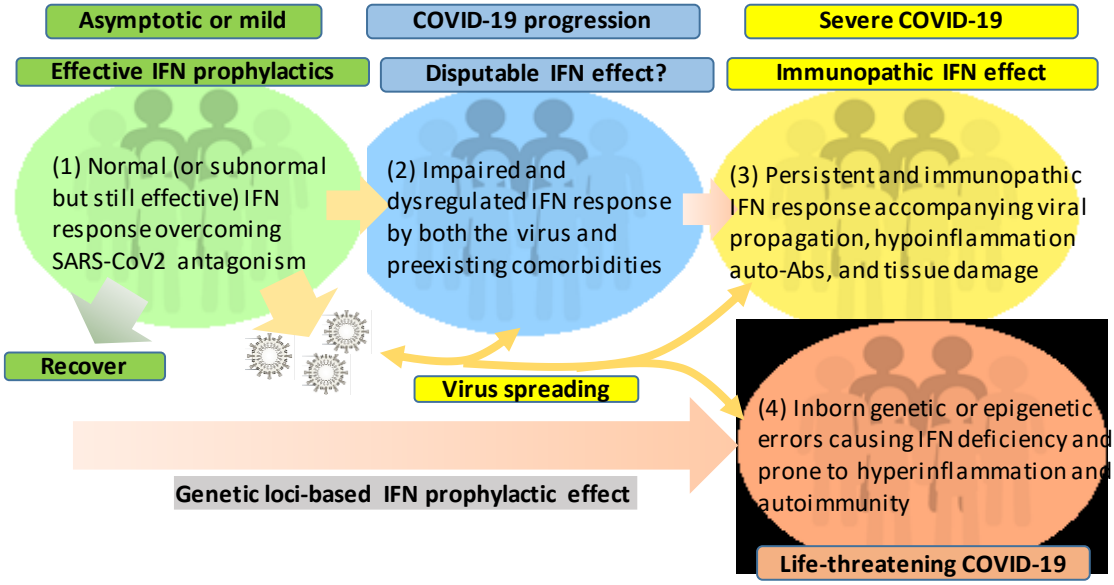

Figure 2. Schematic of patient cohorts of SARS-CoV2 infections based on the severity of COVID-19 and underlying IFN responses. The effective or dysregulated interferon (IFN) response underlies the development of severe and life-threatening COVID-19. The dysregulation of IFN response can be progressively resulted from the viral antagonism/virulence, preexisting comorbidities, gender/age inclination, and exacerbated hyperinflammation, with the extremal genetic flaws impairing IFN signaling pathway. Hence, the prophylactic or therapeutic effect of IFN therapies should be designed and more dependent on the spatiotemporal kinetics of IFN responses during SARS-CoV2 infection and the disease progression. In addition to its evolving antagonism to divert the host IFN response, the high contagiousness of SARS-CoV2 also comes from the efficient virus infection and spreading by the non-hospitalized individuals who are asymptomatic or only having mild signs.

5. Conclusive remarks: Precise IFN response kinetics and application to COVID-19 clinical trials

Effective IFN response, or vice versa IFN dysregulation constitutes a key determinant of COVID-19 prognosis, which also highlights the potential of IFNs for therapeutic intervention [25]. Prophylactic administration of IFNs at the early stage prior to pneumonia progression may antagonize the viral suppression on IFN production and elicit an autonomous antiviral state in affected cells to block viral infection and COVID-19 pathogenesis. An early trial study (NCT04320238) showed that daily IFNα nasal drops enhanced the protection of at-risk health-care workers from COVID-19 over 28 days without noticeable adverse effects [78]. However, the COVID-19 therapeutic effect of IFN treatments remains controversial, with respect to particularly the timing of administration and the pre-existing medical condition according to COVID-19 progression [25,78]. Interferon signaling has intricating crosstalk with multiple inflammatory cytokines including TNF-α, IL-6, because they intersect in using some common intracellular signaling components [16,27]. In this context, prophylactic effect of early IFN application may actually mitigate the CRS through the antiviral and anti-inflammatory effect of some epithelial specific IFN subtypes. However, extensive validation of subtype-specific activity is warranted for a better optimization of IFN's clinical uses [79-81]. By contrast, clinical trials of relevant IL-6, TNF, and JAK STAT inhibitors and blocking antibodies are applicable to the adverse side of dysregulated IFN response, which are devised to mitigate the pathological IFN and pro-inflammatory response sustained in severe COVID19 [79-81]. Recent studies, per significant association of life-threatening COVID-19 with inborn genetic flaws and auto-

Abs that blocking IFN response, genetically and epigenetically, reveal the critical role of IFN dysregulation in severe COVID-19 [51,52]. In most other severe COVID-19 patients without genetic errors in IFN-relevant gene loci, IFN dysregulation is progressively worsen and associated with the situation of proinflammation and immunopathy that prone to autoimmunity [41,61-63,82-84]. In addition, the high correlation of severe COVID-19 with seniority, males and individuals with pre-existing comorbidities, will be plausibly explained by coincidence of IFN dysfunction in these listed situations, which have been reviewed elsewhere [41,82-86]. In addition, ACE2, a key enzyme of RAAS and sneaked as a primary receptor by SARS-CoV2 infection, has been recently identified as a non-canonical ISG like IL-6 in response to IFN-induced epigenetic regulation [18,28-32]. Because the expression and affinity of ACE2 to SARS-CoV2 determines host susceptibility and cell tropism [28-32], the dysregulated IFN response will further deteriorate the viral infection in multiple organs and incapacitate a series of functions regulated through the RAAS axis [30,86]. This will certainly complicate the understanding and application of IFNs particularly for treatment of severe COVID-19 [25,30,86]. All these call for a better understanding of the spatiotemporal characteristics and subtype-specificity of IFN response to SARS-CoV-2 infections, which are warranted to devise IFN-related prophylactics and therapies. It is noteworthy that all designed IFN therapies, which are based on normal IFN signaling, will be not properly functional in individuals who have inborn genetic or auto-immune deficiency of IFN system [52,53]. This will demand for early diagnosis of this kind of genetic and auto-Ab errors in potential and hospitalized patients who are irresponsive to IFN-based treatments [27,52,53].

Author Contributions: P.S. and Y.T. contributed to idea conceptualization, draft preparation and proof reading. P.S. also contributed for depicting figures; Y.S. supervises overall conceptualization, draft writing and figure drawing, review preparation, and funding acquisition.

Funding: This work was supported by USDA NIFA Evans-Allen-1013186 and NIFA 2018-67016-28313 to YS, and in part through reagent sharing of NIFA AFRI 2020-67016-31347 and NSF-IOS-1831988 to YS.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). [Cited October 5, 2020]. Available from: https://coronavirus.jhu.edu/map.html
2. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19). Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-151.
3. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Pdf] - World Health Organization, [Cited October 5, 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
4. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-523.
5. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China [published correction appears in Nature. 2020 Apr;580(7803):E7]. Nature. 2020;579(7798):265-269.
6. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis. 2020;26(7):1470-1477.
7. COVID-19 Pandemic Planning Scenarios [Cited October 5, 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html
8. Courtney EP, Goldenberg JL, Boyd P. The contagion of mortality: A terror management health model for pandemics. Br J Soc Psychol. 2020;59(3):607-617.

9. Age, Sex, Existing Conditions of COVID-19 Cases and Deaths. [Cited July 31, 2020]. Available from: https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/
10. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020;20(7):442-447. doi:10.1038/s41577-020-0348-8
11. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11(1):29.
12. Jutzeler CR, Bourguignon L, Weis CV, et al. Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis [published online ahead of print, 2020 Aug 4]. Travel Med Infect Dis. 2020;101825.
13. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host Microbe. 2020 Jun 10;27(6):992-1000.e3.
14. Silvin A, Chapuis N, Dunsmore G, Goubet AG, Dubuisson A, Derosa L, et al. Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19. Cell. 2020 Sep 17;182(6):1401-1418.e18.
15. Schulte-Schrepping J, Reusch N, Paclik D, Baßler K, Schlickeiser S, Zhang B, et al. Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment. Cell. 2020 Sep 17;182(6):1419-1440.e23.
16. Tian Y, Jennings J, Gong Y, Sang Y. Viral Infections and Interferons in the Development of Obesity. Biomolecules. 2019 Nov 12;9(11):726.
17. Lazear HM, Schoggins JW, Diamond MS. Shared and Distinct Functions of Type I and Type III Interferons. Immunity. 2019 Apr 16;50(4):907-923.
18. Barrat FJ, Crow MK, Ivashkiv LB. Interferon target-gene expression and epigenomic signatures in health and disease. Nat Immunol. 2019 Dec;20(12):1574-1583.
19. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020 Aug 7;369(6504):718-724
20. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell. 2020;181(5):1036-1045.e9
21. Sa Ribero M, Jouvenet N, Dreux M, Nisole S. Interplay between SARS-CoV-2 and the type I interferon response. PLoS Pathog. 2020 Jul 29;16(7):e1008737.
22. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. Cell Host Microbe. 2016;19(2):181-193.
23. Lee, J. S. et al. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. Sci. Immunol. 5, eabd1554 (2020).
24. Lucas, C. et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature https://doi.org/10.1038/s41586-020-2588-y (2020).
25. Lee, J.S., Shin, E. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol 20, 585–586 (2020). https://doi.org/10.1038/s41577-020-00429-3
26. Pairo-Castineira, E.; Clohisey, S.; Klaric, L.; Bretherick, A.; Rawlik, K.; Parkinson, N.; Pasko, D.; Walker, S.; Richmond, A.; Fourman, M.H.; et al. Genetic mechanisms of critical illness in Covid-19. medRxiv 2020, doi:10.1101/2020.09.24.20200048.

27. McCoy, K.; Peterson, A.; Tian, Y.; Sang, Y. Immunogenetic Association Underlying Severe COVID-19. Vaccines 2020, 8, 700.
28. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Cell. 2020;181(5):1016-1035.e19.
29. Sang ER, Tian Y, Miller LC, Sang Y. Epigenetic Evolution of ACE2 and IL-6 Genes as Non-Canonical Interferon-Stimulated Genes Correlate to COVID-19 Susceptibility in Vertebrates. bioRxiv 2020.09.09.273268
30. Alifano M, Alifano P, Forgez P, Iannelli A. Renin-angiotensin system at the heart of COVID-19 pandemic. Biochimie. 2020;174:30-33.
31. Zhuang MW, Cheng Y, Zhang J, et al. Increasing Host Cellular Receptor-Angiotensin-Converting Enzyme 2 (ACE2) Expression by Coronavirus may Facilitate 2019-nCoV (or SARS-CoV-2) Infection [published online ahead of print, 2020 Jun 4]. J Med Virol. 2020;10.1002/jmv.26139.
32. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020;26(5):681-687
33. Berthelot JM, Drouet L, Lioté F. Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? Emerg Microbes Infect. 2020 Dec;9(1):1514-1522.
34. Berthelot JM, Lioté F. COVID-19 as a STING disorder with delayed over-secretion of interferon-beta. EBioMedicine. 2020 Jun;56:102801.
35. Dunphy G, Flannery SM, Almine JF, Connolly DJ, Paulus C, Jønsson KL, Jakobsen MR, Nevels MM, Bowie AG, Unterholzner L. Non-canonical Activation of the DNA Sensing Adaptor STING by ATM and IFI16 Mediates NF-κB Signaling after Nuclear DNA Damage. Mol Cell. 2018 Sep 6;71(5):745-760.e5.
36. Majoros A, Platanitis E, Kernbauer-Hölzl E, Rosebrock F, Müller M, Decker T. Canonical and Non-Canonical Aspects of JAK-STAT Signaling: Lessons from Interferons for Cytokine Responses. Front Immunol. 2017 Jan 26;8:29.
37. Christopher J. Neufeldt, Berati Cerikan, Mirko Cortese, et al., SARS-CoV-2 infection induces a pro-inflammatory cytokine response through cGAS-STING and NF-κB. bioRxiv 2020.07.21.212639.
38. Motwani, M., Pesiridis, S. & Fitzgerald, K.A. DNA sensing by the cGAS–STING pathway in health and disease. Nat Rev Genet 20, 657–674 (2019).
39. Chen X, Yang X, Zheng Y, Yang Y, Xing Y, Chen Z. SARS coronavirus papain-like protease inhibits the type I interferon signaling pathway through interaction with the STING-TRAF3-TBK1 complex. Protein Cell. 2014 May;5(5):369-81.
40. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. Nat Rev Immunol. 2015 Feb;15(2):87-103.
41. Crow MK, Olferiev M, Kirou KA. Type I Interferons in Autoimmune Disease. Annu Rev Pathol. 2019 Jan 24;14:369-393.
42. Hijano DR, Vu LD, Kauvar LM, Tripp RA, Polack FP, Cormier SA. Role of Type I Interferon (IFN) in the Respiratory Syncytial Virus (RSV) Immune Response and Disease Severity. Front Immunol. 2019 Mar 26;10:566.
43. Andreakos E, Tsiodras S. COVID-19: lambda interferon against viral load and hyperinflammation. EMBO Mol Med. 2020 Jun 8;12(6):e12465.

44. Broggi A, Ghosh S, Sposito B, Spreafico R, Balzarini F, Lo Cascio A, Clementi N, De Santis M, Mancini N, Granucci F, Zanoni I. Type III interferons disrupt the lung epithelial barrier upon viral recognition. Science. 2020 Aug 7;369(6504):706-712.
45. Major J, Crotta S, Llorian M, McCabe TM, Gad HH, Priestnall SL, Hartmann R, Wack A. Type I and III interferons disrupt lung epithelial repair during recovery from viral infection. Science. 2020 Aug 7;369(6504):712-717.
46. Grajales-Reyes GE, Colonna M. Interferon responses in viral pneumonias. Science. 2020 Aug 7;369(6504):626-627.
47. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, Soucy JR, Daneman N. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020 Jul 22:S1198-743X(20)30423-7.
48. Chen X, Liao B, Cheng L, et al. The microbial coinfection in COVID-19. Appl Microbiol Biotechnol. 2020;104(18):7777-7785.
49. Sang Y, Rowland RR, Blecha F. Molecular characterization and antiviral analyses of porcine type III interferons. J Interferon Cytokine Res. 2010 Nov;30(11):801-7.
50. Jennings J, Sang Y. Porcine Interferon Complex and Co-Evolution with Increasing Viral Pressure after Domestication. Viruses. 2019 Jun 15;11(6):555.
51. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020 Sep 24:eabd4570.
52. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020 Sep 24:eabd4585.
53. Fung KY, Mangan NE, Cumming H, Horvat JC, Mayall JR, Stifter SA, De Weerd N, Roisman LC, Rossjohn J, Robertson SA, Schjenken JE, Parker B, Gargett CE, Nguyen HP, Carr DJ, Hansbro PM, Hertzog PJ. Interferon-ε protects the female reproductive tract from viral and bacterial infection. Science. 2013 Mar 1;339(6123):1088-92.
54. LaFleur DW, Nardelli B, Tsareva T, Mather D, Feng P, Semenuk M, Taylor K, Buergin M, Chinchilla D, Roshke V, Chen G, Ruben SM, Pitha PM, Coleman TA, Moore PA. Interferon-kappa, a novel type I interferon expressed in human keratinocytes. J Biol Chem. 2001 Oct 26;276(43):39765-71.
55. Vallbracht A, Treuner J, Flehmig B, Joester KE, Niethammer D. Interferon-neutralizing antibodies in a patient treated with human fibroblast interferon. Nature. 1981 Feb 5;289(5797):496-7.
56. Panem S, Check IJ, Henriksen D, Vilcek J. Antibodies to alpha-interferon in a patient with systemic lupus erythematosus. J Immunol. 1982 Jul;129(1):1-3.
57. Meager A, Visvalingam K, Peterson P, Möll K, Murumägi A, Krohn K, Eskelin P, Perheentupa J, Husebye E, Kadota Y, Willcox N. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med. 2006 Jul;3(7):e289.
58. Kim GU, Kim MJ, Ra SH, Lee J, Bae S, Jung J, Kim SH. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. Clin Microbiol Infect. 2020 Jul;26(7):948.e1-948.e3.
59. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. Ann Intern Med. 2020 Sep 1;173(5):362-367.
60. Zhao H, Lu X, Deng Y, Tang Y, Lu J. COVID-19: asymptomatic carrier transmission is an underestimated problem. Epidemiol Infect. 2020 Jun 11;148:e116.
61. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY). 2020 Apr 8;12(7):6049-6057.

62. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. N Engl J Med. 2020 Jun 25;382(26):2534-2543.
63. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 May 26;323(20):2052-2059.
64. Agrawal, A. Dendritic Cell-Airway Epithelial Cell Cross-Talk Changes with Age and Contributes to Chronic Lung Inflammatory Diseases in the Elderly. *Int. J. Mol. Sci.* **2017**, *18*, 1206.
65. Prakash, S.; Agrawal, S.; Vahed, H.; Ngyuen, M.; BenMohamed, L.; Gupta, S.; Agrawal, A. Dendritic cells from aged subjects contribute to chronic airway inflammation by activating bronchial epithelial cells under steady state. *Mucosal Immunol*. **2014**, *7*, 1386–1394.
66. Chen, J.; Kelley, W.J.; Goldstein, D.R. Role of Aging and the Immune Response to Respiratory Viral Infections: Potential Implications for COVID-19. *J. Immunol*. **2020**, *205*, 313–320.
67. Webb, K.; Peckham, H.; Radziszewska, A.; Menon, M.; Oliveri, P.; Simpson, F.; Deakin, C.T.; Lee, S.; Ciurtin, C.; Butler, G.; et al. Sex and Pubertal Differences in the Type 1 Interferon Pathway Associate With Both X Chromosome Number and Serum Sex Hormone Concentration. Front. Immunol. 2019, 9, 3167.
68. Capone, I.; Marchetti, P.; Ascierto, P.A.; Malorni, W.; Gabriele, L. Sexual Dimorphism of Immune Responses: A New Perspective in Cancer Immunotherapy. Front. Immunol. 2018, 9, 552.
69. Chlamydas, S.; Papavassiliou, A.G.; Piperi, C. Epigenetic mechanisms regulating COVID-19 infection. Epigenetics 2020, 30, 1–8.
70. Sawalha, A.H.; Zhao, M.; Coit, P.; Lu, Q. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin. Immunol. 2020, 215, 108410.
71. Netea, M.G.; Giamarellos-Bourboulis, E.J.; Domínguez-Andrés, J.; Curtis, N.; van Crevel, R.; van de Veerdonk, F.L.; Bonten, M. Trained Immunity: A Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection. Cell 2020, 181, 969–977.
72. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr. 2020 Jun;10(6):537-540.
73. Becker RC. COVID-19-associated vasculitis and vasculopathy. J Thromb Thrombolysis. 2020 Oct;50(3):499-511.
74. Berger JR. COVID-19 and the nervous system. J Neurovirol. 2020 Apr;26(2):143-148.
75. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767-783.
76. Shields LE, Jennings J, Liu Q, Lee J, Ma W, Blecha F, Miller LC, Sang Y. Cross-Species Genome-Wide Analysis Reveals Molecular and Functional Diversity of the Unconventional Interferon-ω Subtype. Front Immunol. 2019 Jun 25;10:1431.
77. Experimental Trial of rhIFNα Nasal Drops to Prevent 2019-nCOV in Medical Staff. [Cited October 5, 2020]. Available at https://clinicaltrials.gov/ct2/show/NCT04320238.
78. Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, Wang ZH, Tebbutt SJ, Kollmann TR, Fish EN. Interferon-α2b Treatment for COVID-19. Front Immunol. 2020 May 15;11:1061. doi: 10.3389/fimmu.2020.01061.

79. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607-613.
80. Ucciferri C, Vecchiet J, Falasca K. Role of monoclonal antibody drugs in the treatment of COVID-19. World J Clin Cases. 2020 Oct 6;8(19):4280-4285.
81. Spinelli FR, Conti F, Gadina M. HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. Sci Immunol. 2020 May 8;5(47):eabc5367.
82. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, Alijotas-Reig J, Zinserling V, Semenova N, Amital H, Shoenfeld Y. Covid-19 and autoimmunity. Autoimmun Rev. 2020 Aug;19(8):102597.
83. Costello F, Dalakas MC. Cranial neuropathies and COVID-19: Neurotropism and autoimmunity. Neurology. 2020 Aug 4;95(5):195-196.
84. Li G, Ju J, Weyand CM, Goronzy JJ. Age-Associated Failure To Adjust Type I IFN Receptor Signaling Thresholds after T Cell Activation. J Immunol. 2015 Aug 1;195(3):865-74.
85. Choubey D, Moudgil KD. Interferons in autoimmune and inflammatory diseases: regulation and roles. J Interferon Cytokine Res. 2011 Dec;31(12):857-65.
86. Crowley SD, Rudemiller NP. Immunologic Effects of the Renin-Angiotensin System. J Am Soc Nephrol. 2017 May;28(5):1350-1361.