ANNUAL REVIEWS

Annual Review of Immunology

Interfering with Interferons: A Critical Mechanism for Critical COVID-19 Pneumonia

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Annu. Rev. Immunol. 2023. 41:561–85

The *Annual Review of Immunology* is online at immunol.annualreviews.org

https://doi.org/10.1146/annurev-immunol-101921-050835

*See Author Contributions statement

Keywords

COVID-19, SARS-CoV-2, type I interferon, human genetics, anticytokine autoantibodies

Abstract

Infection with SARS-CoV-2 results in clinical outcomes ranging from silent or benign infection in most individuals to critical pneumonia and death in a few. Genetic studies in patients have established that critical cases can result from inborn errors of TLR3- or TLR7-dependent type I interferon immunity, or from preexisting autoantibodies neutralizing primarily IFN-α and/or IFN-ω. These findings are consistent with virological studies showing that multiple SARS-CoV-2 proteins interfere with pathways of induction of, or response to, type I interferons. They are also congruent with cellular studies and mouse models that found that type I interferons can limit SARS-CoV-2 replication in vitro and in vivo, while their absence or diminution unleashes viral growth. Collectively, these findings point to insufficient type I interferon during the first days of infection as a general mechanism underlying critical COVID-19 pneumonia, with implications for treatment and directions for future research.

COVID-19

We are now into the third year of the COVID-19 pandemic, with no clear end in sight. At least 6.6 million people have died of COVID-19 (**https://coronavirus.jhu.edu/map.html**, accessed December 2022), and the death toll is probably much higher. The virus responsible for these deaths, SARS-CoV-2, is an RNA respiratory virus and the third known highly virulent human-tropic coronavirus (1). Up to 85% of unvaccinated individuals develop silent infection or benign upper respiratory disease, and about 10% develop nonhypoxemic pneumonia (2). Hypoxemic pneumonia strikes about 5%, a third of whom require admission to an intensive care unit (ICU) for mechanical ventilation (2), with a global infection fatality rate between 0.3% and 1% across age, gender, and ethnicity (3). The risk of hospitalization and death is strongly age dependent: It doubles every 5 years and is 10,000 greater at 85 than 5 years old (4). Other clinical forms of SARS-CoV-2 infection include multisystem inflammatory syndrome in children (MIS-C) (5), pernio (i.e., COVID toes) (6), and postacute COVID-19 syndrome (i.e., long COVID) (7).

Over the last three years, multiple variants of SARS-CoV-2 have emerged and spread, often with increasing transmissibility but with no clear evidence of increased virulence (8). RNA vaccines, developed in a record-breaking feat of less than one year, have provided protection from life-threatening pneumonia in most but not all vaccinees, while other types of vaccines have been less effective (9). Even RNA vaccines, however, do not prevent infection per se, as vaccinated individuals can be infected and transmit the virus. Therapies administered to patients with hypoxemic pneumonia were supportive for about one year into the pandemic, with specific antivirals and monoclonal antibodies becoming available only in 2021 (10). Despite these developments, much remains to be done to better understand SARS-CoV-2-related disease mechanisms and improve the management of patients.

The most puzzling enigma over the last three years has been the extremely broad spectrum of interindividual variability during infection, especially in unvaccinated individuals. Using an approach similar to one that has been successful for other common infectious diseases (11), we launched the COVID Human Genetic Effort (**https://www.covidhge.com**) to discover the molecular, cellular, and immunological determinants of the various clinical forms of SARS-CoV-2 infection (12). We also aimed to discover the molecular and cellular basis of resistance to infection per se (13). Our first achievement has been the discovery that insufficient type I interferon immunity is a key driver of critical COVID-19 pneumonia in at least 15–20% of patients, highlighting the importance of type I interferon immunity for potential therapeutic interventions. We will not discuss here our second, more recent achievement, which has been the identification of inborn errors of the OAS–RNase L pathway in children with MIS-C (14).

TYPE I INTERFERONS AND THEIR FUNCTIONS

Interferon was originally discovered by Isaacs & Lindenmann in 1957 during studies of virus interference (15). They identified a substance newly released from influenza virus–infected chick cells that was able to suppress a second viral infection and named it interferon to distinguish it from viral proteins (15). We now know that interferons are divided into three families (types I, II, and III) based on their sequence similarity and the receptor complexes through which they signal (16–19). In humans, there are 17 type I interferons (13 subtypes of IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω), a single type II interferon (IFN-γ), and 3 type III interferons (IFN-λ). Most if not all human cells can produce type I interferons, whose receptor is also ubiquitously expressed. Human type I interferons have been shown to control infections by many different viruses in vitro in diverse cell types (16, 20). The protective functions of IFN-λ against some virus infections in vitro in a more restricted range of cell types are also well-recognized, particularly in epithelial

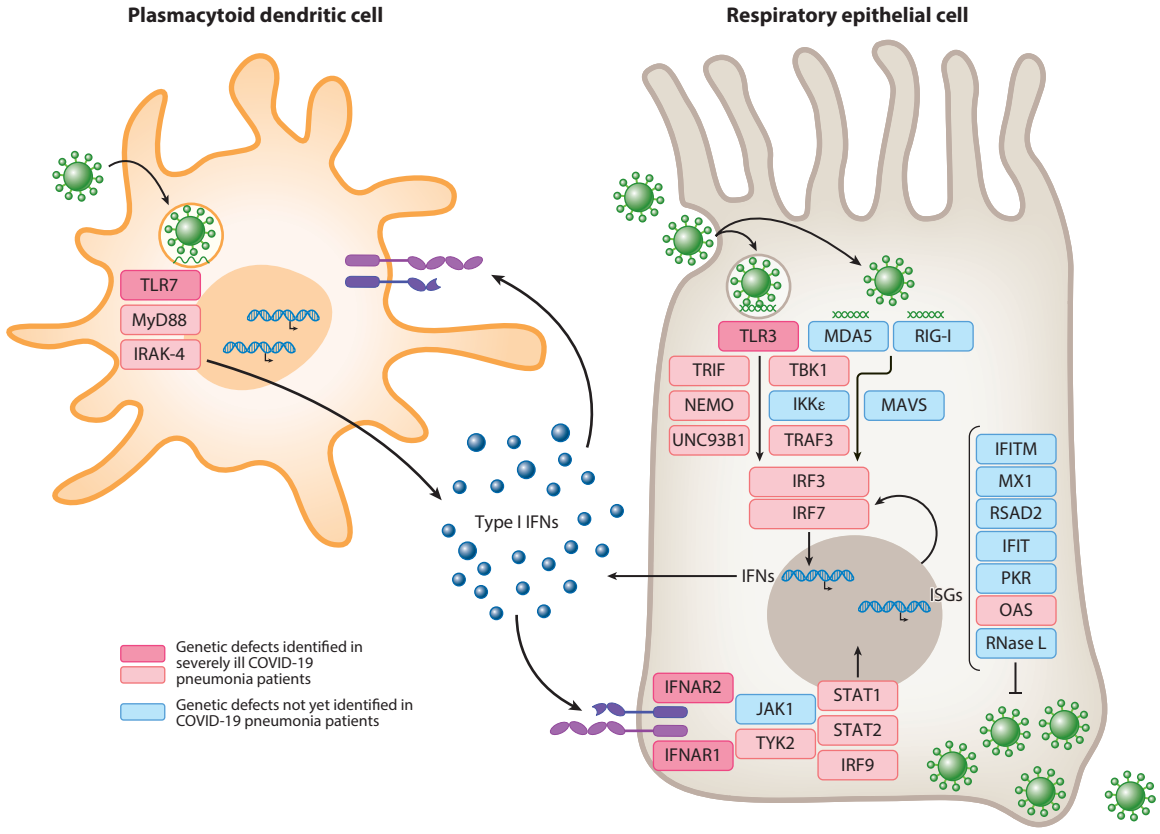

Figure 1

Pathways of virus-induced type I interferon immunity and genetic defects found in COVID-19 patients. As detailed in the text, sensors of viral RNAs include TLR3 and TLR7 (the latter in plasmacytoid dendritic cells) or RLR helicases (MDA5, RIG-I), which trigger signaling cascades that converge upon IRF3 and IRF7 for type I interferon production. The secreted type I interferons bind to IFNAR1 and IFNAR2 (forming type I interferon receptors) to induce via ISGF-3 (STAT1, STAT2 and IRF9 trimer) host gene transcription of ISGs, which through various mechanisms suppress virus replication. The plasmacytoid dendritic cell has been simplified to depict only the TLR7-proximal signaling events. Genetic defects identified in severely ill COVID-19 pneumonia patients are indicated by pink boxes, whereas those that have not yet been identified in COVID-19 pneumonia patients are indicated in blue boxes. RNase L genetic defects have been identified in MIS-C patients but not in COVID-19 pneumonia patients so are not highlighted here (14). Abbreviations: IFIT, interferon-induced protein with tetratricopeptide repeats; IFITM, interferon-induced transmembrane protein; IFN, interferon; IFNAR1, interferon alpha and beta receptor subunit 1; IRF3, interferon regulatory factor 3; ISG, interferon-stimulated gene; ISGF-3, interferon-stimulated gene factor 3; MIS-C, multisystem inflammatory syndrome in children; RIG-I, retinoic acid–inducible gene I; RLR, RIG-I-like receptor; TLR3, Toll-like receptor 3.

cells (21). By contrast, type II interferon is produced by leukocytes and primarily functions as a macrophage-activating factor rather than in antiviral immunity, and it is not discussed further in this review (22). We will also focus our discussion on type I interferons (**Figure 1**), whose role in the pathogenesis of COVID-19 is now established.

In most resting cells, type I/III interferons are expressed at very low levels, but their expression is rapidly induced when viral products are detected by host virus sensors in various subcellular compartments (23). Within endosomal compartments, double-stranded RNA (dsRNA) is recognized by Toll-like receptor 3 (TLR3), single-stranded RNA (ssRNA) by TLR7/8, and unmethylated CpG DNA by TLR9. Activation of TLR7–9 leads to induction of type I/III interferon

mainly through the MyD88- and IRAK-4-dependent signaling pathway, while activation of TLR3 proceeds through the TIR-domain-containing adaptor-inducing IFN-β (TRIF)-dependent signaling pathway. Within the cytosol, dsRNA is sensed by the retinoic acid–inducible gene I (RIG-I)-like receptors (RLRs)-MAVS pathway, while dsDNA is sensed by the cGMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway (24, 25). These different signaling pathways converge upon interferon regulatory factor 3 (IRF3) and IRF7, which are key positive regulators of type I/III interferon induction (26). Upon upstream activation, IKKε and TBK-1 phosphorylate IRF3 and IRF7, which homodimerize or heterodimerize to activate type I/III interferon expression. IRF7 is expressed at low basal levels in cells other than plasmacytoid dendritic cells (pDCs) but can be upregulated by interferon signaling during viral infections, leading to a positive feedback loop that amplifies interferon responses (26). Type I interferons can also be induced by sensors recognizing self RNA/DNA when aberrantly released from damaged cells or mitochondria, thereby instigating the development of type I interferonopathies (23, 27).

Type I interferons signal through heterodimeric type I interferon receptor (IFNAR), composed of the IFNAR1 and IFNAR2 subunits, which are ubiquitously expressed on all nucleated cells (17, 28, 29). Binding of this receptor complex activates the constitutively associated kinases JAK1 and TYK2, which phosphorylate STAT1 and STAT2, leading to STAT1-STAT2 heterodimerization and then association with the DNA-binding component IRF9 (30). The STAT1-STAT2-IRF9 heterotrimeric transcription factor interferon-stimulated gene factor 3 (ISGF-3) complex binds interferon-stimulated response elements (ISRE) in the promoter regions of interferon-stimulated genes (ISGs) to turn on or off their expression (28, 29). Different type I interferon subtypes have different binding affinities to the IFNAR1/2 receptor complex, resulting in different signal strengths and different sensitivities to negative regulators (30). For example, with the highest affinity among all type I interferons, IFN-β exerts more robust antiviral effects. Its tighter binding to IFNAR1 can apparently elicit in some experimental conditions IFNAR2-independent signals (30, 31), and its own activity is unaffected by USP18-mediated desensitization while impairing reactivation of IFN-α signaling (32). Strikingly, IFN-ε and IFN-κ have at least 1,000-fold less activity than the other subtypes (33, 34).

By contrast, type III interferons signal through a different heterodimeric receptor complex, composed of the IFNLR1 (IL-28Rα) and IL-10R2 (also termed IL-10Rβ) subunits, to activate the JAK-STAT pathway for many of the same ISGs (17, 28, 29). As with the type I interferons, type III interferons display different receptor affinities, but overall binding affinities for type III interferons to their receptors are lower than those of type I interferons to their cognate receptors, resulting in type III interferons being generally less antiviral and less inflammatory than type I interferons (17). Furthermore, IFNLR1 expression is restricted to epithelial cells in the intestinal, respiratory, and female reproductive tracts, correlating with preferential type III interferon induction at mucosal surfaces (35, 36). Growing evidence in mouse models of infection suggests that type I and III interferons cooperate in vivo, with type III interferons serving to contain virus spread to initial sites of infection at mucosal surfaces, and type I interferons importantly protecting against systemic spread of virus (37, 38). It is unclear whether this synergic dichotomy holds in humans.

Type I/III interferons can induce or regulate the transcription of target genes (28, 29). Most human ISGs are thought to be antiviral, although the first inborn errors of human ISGs were surprisingly found in patients without viral diseases but with type I interferonopathy due to mutations in *ISG15* or *USP18* (39, 40). Following type I interferon signaling, hundreds of ISGs are rapidly induced that globally exert antiviral activities, albeit through distinct molecular mechanisms (28, 29). ISGs include some sensors, IRFs, and several signal-transducing proteins such as STAT1/2. They are usually expressed at very low levels in resting cells but are upregulated by interferon signaling upon viral infections. ISGs sensitize host cells, including bystander uninfected cells, to

enhance virus detection, amplify interferon production, and reinforce interferon responses (28, 29). ISGs can directly interfere with pathways required for the life cycles of viruses, such as preventing virion entry into host cells [e.g., interferon-induced transmembrane proteins (IFITMs)] and trafficking into the nucleus (e.g., MX1), halting virus genome replication (e.g., RSAD2) and virus protein translation [e.g., interferon-induced proteins with tetratricopeptide repeats (IFITs), PKR], and degrading virus RNAs or genomes (e.g., OAS, RNase L) (41–44). Except for MX1 in which rare loss-of-function variants conferred increased replication of and susceptibility to influenza virus (45), these findings in vitro and in mouse models await confirmation in vivo in humans. Besides suppressing viral replication, interferons modulate immune responses by producing proinflammatory chemokines and altering immune cell functions (20, 46). Effects include increasing antigen presentation by macrophages and dendritic cells, as well as directly activating natural killer cells, T cells, and B cells (47–50). Interferons also exert antiproliferative activity by blocking cell cycle and inducing apoptosis (51, 52). These immunomodulatory and other effects require much higher concentrations of and prolonged stimulation by interferons than what is required for antiviral activities (30).

SARS-CoV-2-ENCODED PROTEINS ANTAGONIZE THE HOST TYPE I INTERFERON ANTIVIRAL RESPONSE

Early studies demonstrated that exogenously added type I interferons suppress SARS-CoV-2 replication in vitro within various cell lines (53–55). These included respiratory cell lines such as the human bronchial epithelial cell line Calu-3, which expresses ACE2 and TMPRSS2 (required for virus entry and viral Spike-protein priming) at levels sufficient for replicative infection by SARS-CoV-2, and which can produce and respond to type I interferons. Furthermore, the virus-restricting effects of type I interferon in vitro are apparent even when it is added after infection (54). By contrast, treatment of Calu-3 cells with ruxolitinib, a JAK inhibitor that interferes with downstream type I interferon signaling, increases SARS-CoV-2 replication (53). These results support the importance of type I interferons in limiting SARS-CoV-2 replication and suggest that interfering with type I interferon during early infection could impair control of viral replication.

Several of these studies also examined responses to type III interferons, which predominantly target epithelial cells. Type III interferons are produced not only at the initial site of infection in the respiratory tract but also in the gastrointestinal tract, which may function as a persisting reservoir for infectious SARS-CoV-2. In Calu-3 cells, human colonic cell lines, and colonic organoid culture systems, exogenously added type III interferons, like type I interferons, suppress SARS-CoV-2 replication in vitro (53, 55). However, SARS-CoV-2 replication increases to a greater extent in intestinal epithelial cells deficient for the type III interferon receptor versus the type I interferon receptor (55). Although SARS-CoV-2 is predominantly transmitted by the respiratory route rather than through the gastrointestinal tract, these results suggest that endogenously produced type III interferons may contribute to virus suppression in the gastrointestinal tract, including at later times when adaptive immunity is also active and predominates.

Compared with SARS-CoV, which is responsible for the first documented coronavirus pandemic, SARS-CoV-2 appears more sensitive to the virus-restricting effects of type I interferon in respiratory cells (53). This differential sensitivity raises the possibility that the two viruses diverged in their ability to antagonize the host antiviral type I interferon response. SARS-CoV encodes proteins such as NSP3, ORF3b, and ORF6, which can subvert type I interferon immunity by deubiquitinating ISG15 (56), interfering with IRF3 phosphorylation/nuclear translocation (57), or blocking STAT1 nuclear transport (58). Similar mechanisms of type I interferon antagonism have also been reported for SARS-CoV-2 viral proteins (59, 60). Interestingly, ORF6

from SARS-CoV-2 shows modest sequence identity (<70%) when compared with ORF6 from other coronaviruses including SARS-CoV. Thus, an ORF6 less effective at antagonizing type I interferons might account for SARS-CoV-2's relatively increased sensitivity to type I interferons. This explanation is supported by a recent elegant study that used recombinant viruses having a SARS-CoV backbone and encoding either wild-type ORF6 from SARS-CoV-2 or a mutated nonfunctional ORF6 from SARS-CoV (61). Infection of Calu-3 cells with these recombinant viruses, when compared to infection with SARS-CoV, induced higher levels of type I interferon–dependent genes along with decreased viral replication.

The differential ability to antagonize type I interferon responses may extend to different SARS-CoV-2 subtypes as they continue to evolve. Amino acid substitutions in the C-terminal region of SARS-CoV-2 ORF6, particularly those that remove charged residues, decrease the ability to antagonize type I interferon responses, as shown in overexpression-reporter assay systems (59, 60). Reciprocally, mutations that introduce charged residues in this region increase the ability to antagonize type I interferon responses, and several such mutations have already been identified in large sequencing databases (61). As an RNA virus, SARS-CoV-2 has a relatively high mutation rate, so changes can rapidly accumulate, particularly within individuals having defective immunity (62–66). From a practical standpoint, this means that dynamic changes in the virus genome that alter its ability to antagonize human type I interferon immunity, along with germline mutations in humans, might influence disease severity and could potentially explain the variable disease penetrance in humans with monogenic defects in type I interferon immunity. For this reason, future research that combines sequencing within any given individual of SARS-CoV-2 genomes in parallel with human genome sequencing could be informative.

MOUSE MODELS OF SARS-CoV-2 INFECTION: VARIABLE IMPACTS OF TYPE I INTERFERON ON DISEASE OUTCOME

As SARS-CoV-2 is not a natural mouse pathogen, various approaches have been taken to facilitate its use in mice (67). These include transgenic or adenovirus vector–delivered expression of the human ACE2 (hACE2) receptor to permit infection and development of mouse-adapted strains of SARS-CoV-2. The advantage of such approaches is the availability of knockout strains, monoclonal antibodies, and other reagents that enable in vivo dissection of the contributions of type I interferons and other molecules, as well as those of leukocytic and nonleukocytic cell types, for viral replication, disease pathology, and survival. A caveat is that the mouse models do not mimic human infection well, due to differences resulting from ectopic expression of hACE2. For example, such mice show SARS-CoV-2 replication in the respiratory tract and central nervous system but not in the gastrointestinal tract and kidney, unlike what is observed in natural infections of humans (68).

Previous studies of SARS-CoV infections in hACE2-expressing mice have established a role for early type I interferon responses in preventing severe disease, with modest effects on limiting early viral replication (69, 70). However, studies of SARS-CoV-2 infections using similar mouse models have been less clear. One study from Sun et al. (71) showed increased viral replication in the lungs at early times after infection in Ifnar1- or Stat1-deficient mice, indicating that type I interferon contributed to early antiviral immunity. However, lung inflammation was decreased in the former while increased (along with increased weight loss) in the latter. This disparity raised the possibility that type III interferon responses, which are also compromised by Stat1 deficiency, might normally have a role in limiting disease. Stat1 deficiency also impairs cellular responses to type II interferon and IL-27. By contrast, a second study from Hassan et al. (72) showed marginally increased viral replication in the lung of Stat1-deficient mice, and treatment of wild-type mice with anti-Ifnar1 blocking antibodies also did not increase viral replication in the lung but did increase weight loss

and lung inflammation. Further complicating the interpretation, a third study from Israelow et al. (73) showed viral replication was also unchanged in the lungs of Ifnar- or Irf3/7-deficient mice, while T cell and monocyte/macrophage infiltration was not increased but decreased. The latter results raise the possibility that any positive effects of type I interferons on limiting viral replication might be counteracted by negative effects of type I interferon on inflammation, which could be required for optimal antiviral immunity in the whole animal. The different results among these early studies may reflect multiple factors such as efficiency of hACE2 expression, virus isolate, dose of virus used in the experimental infections, timing when viral replication was measured, age, sex, and mouse strain.

Of these factors, genetic background has rarely been considered in mouse studies, which are usually conducted using inbred C57BL/6 mice. A recent study by Robertson et al. (74) comprehensively examined SARS-CoV-2 infections in hACE2-transgenic F1 offspring of 10 mouse strains (including Collaborative Cross founder mice), which collectively cover over 90% of this species' genetic variability. The phenotypic responses among the mice showed wide variability, with different patterns of weight loss, survival, and sex-dependent outcomes. Several different patterns were observed depending upon the strain: high sensitivity with high and prolonged viral replication in lungs and brain (e.g., C57BL/6), resistance with low viral replication in lung and elsewhere (e.g., BALB/c), or sex-dependent resistance that was not correlated with level of viral replication (e.g., WSB). Interestingly, increased inflammatory infiltrates in the lung correlated with disease sensitivity for some strains but were also observed in some resistant strains. Additionally, several different patterns were observed when type I interferon responses were measured at early times after infection: high levels correlating with resistance, low levels correlating with sensitivity, or high levels discordant with lung pathology and sensitivity. Overall, there generally appeared to be correlation between early type I interferon production, control of viral replication, and outcome, but in a few strains, other mechanisms apart from production of type I interferon may also determine outcome. These might involve cellular responses to type I interferons, i.e., the range and levels of ISGs induced.

Given the potential immunomodulatory role of type I interferons, the disparate mouse strain study additionally characterized production in the lung of cytokines and chemokines in the different F1 crosses (74). Resistant versus sensitive mice had different patterns and kinetics of production, with resistant mice showing higher levels of inflammasome-mediated cytokines, Th1-type cytokines, and chemokines at early times after infection. By contrast, sensitive mice made less of these products at early times but continued to produce them at later times. Furthermore, sensitive mice also showed increased production at later times of IL-10 and the myeloid chemoattractant CCL4. Overall, these results are consistent with the idea that type I interferon not only exerts direct antiviral effects on viral replication but also has immunomodulatory or proinflammatory effects, and the idea that dysregulated type I interferon responses can contribute to disease manifestations depending on timing and location during infection (**Figure 2**). This is consistent with what has been demonstrated in mouse models of SARS-CoV infection, where type I interferon provided early is protective, but when delayed it causes severe disease by recruiting monocytes into the lung, which differentiate into macrophages producing proinflammatory cytokines (69, 70). Although similar studies have not been conducted for SARS-CoV-2, elevated type I interferon production was shown to contribute to pathology in a humanized mouse model of chronic SARS-CoV-2 infection (75). In that study, human macrophages were capable of being infected with SARS-CoV-2, treatment with anti-IFNAR antibodies decreased weight loss and lung inflammation, and anti-IFNAR antibodies in combination with the antiviral remdesivir also decreased proinflammatory gene expression. Thus, under some circumstances elicited by SARS-CoV-2 infections, the type I interferon responses are pathogenic rather than protective.

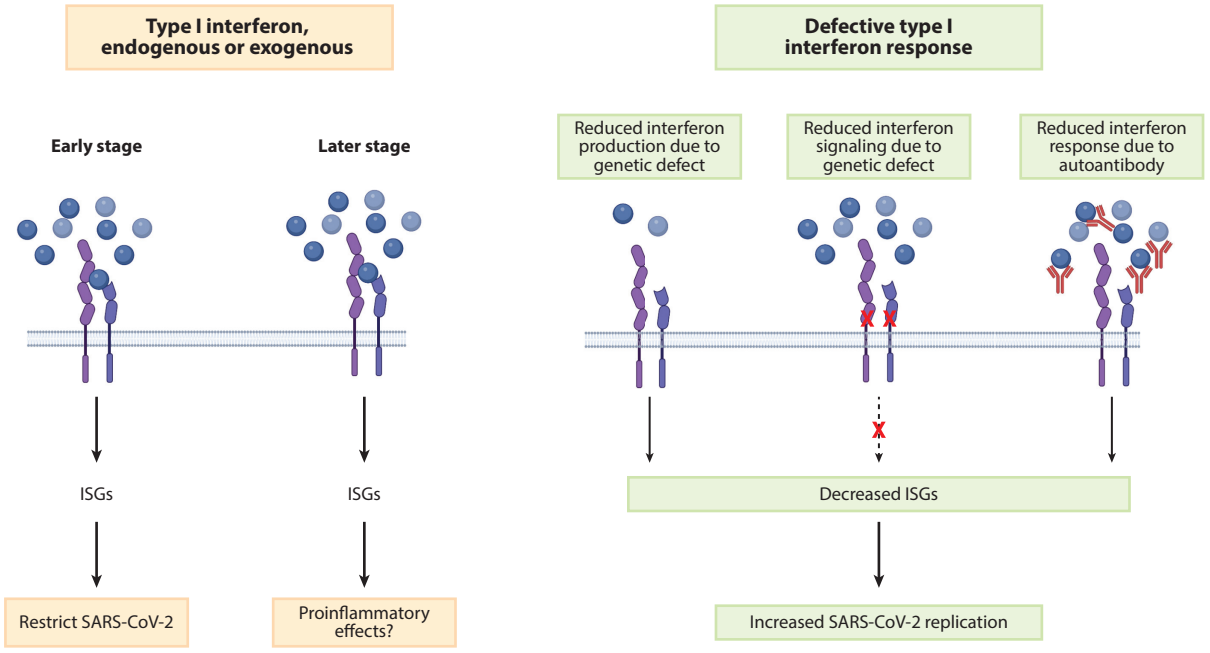

Figure 2

Critical role of type I interferon immunity for outcome of SARS-CoV-2 infection. At an early stage during SARS-CoV-2 infection, endogenously produced type I interferons can elicit antiviral responses that efficiently suppress SARS-CoV-2 replication with minimal pathology. Treatment with type I interferons, if provided sufficiently early, can do the same. However, sustained production of type I interferons during chronic SARS-CoV-2 infections, or delayed treatment with type I interferons, can damage the lungs, probably through enhanced proinflammatory effects. Defective type I interferon immunity in humans, resulting from genetic mutations impairing production or responses to type I interferons or from autoantibodies neutralizing type I interferons, increases SARS-CoV-2 replication and predisposes to life-threatening COVID-19. Abbreviation: ISG, interferon-stimulated gene. Figure adapted from images created with Biorender.com.

The recent comparisons showing high variability among different mouse strains are especially relevant for human studies of SARS-CoV-2 susceptibility, which are typically conducted in populations of various ancestries. It is easy to see how patients with different genetic backgrounds could exhibit differences in the relative contribution of type I interferons versus other factors in determining clinical outcome, especially if type I interferon effects can also be beneficial or detrimental depending on the stage of infection and tissue site. For some patient cohorts, the resulting noise may confound genetic association studies, emphasizing the increased importance of functional studies.

GENETIC LESIONS AFFECTING THE TYPE I INTERFERON PATHWAY IN HUMANS

Production of type I interferons occurs early during acute virus infections in humans, and SARS-CoV-2 is no exception. Most critically ill COVID-19 patients showed IFN-α2 in plasma peaking within 10 days of symptom onset and declining to below detection by 30 days (76). However, approximately 20% of patients had no detectable IFN-α2 within 20 days. This latter group of patients had somewhat worse outcome, with greater likelihood of requiring mechanical ventilation and longer duration of ICU stay (76). In another study examining a small series of patients with differing severities of COVID-19, IFN-α2 levels, biological type I interferon

activity, and downstream ISG score in the blood were lowest for the critically ill, intermediate for those severely ill, and highest among those mildly/moderately ill (77). These measures of type I interferon correlated inversely with plasma virus load and circulating inflammatory mediators such as IL-6 and TNF. Hence, these early observations suggested that insufficient type I interferons led to poor control of SARS-CoV-2 replication and in turn immunopathologic inflammation resulting in life-threatening disease. Descriptive and correlative studies of COVID-19 or other infectious diseases, however, suffer from the inevitable problem that the anomalies observed may be a cause of disease or a consequence of infection or disease. An alternative interpretation of these findings is that disseminated viral infection in patients with the most severe forms of COVID-19 would exhaust type I interferon production in infected tissues.

Human genetic studies searching for inborn errors of immunity (IEIs) in patients with critical COVID-19 have clarified the contribution of type I interferon to infection outcome (**Figure 1**). Building on the prior identification of IEIs of TLR3-dependent type I interferon in otherwise healthy children with critical influenza pneumonia (78), we undertook a candidate gene approach to test the hypothesis that critical influenza and critical COVID-19 pneumonia may be allelic at some of the 13 influenza susceptibility loci (79). This approach was successful, showing an enrichment in variants predicted to be loss-of-function (pLOF) in adult patients, when compared with individuals with silent or mild infection. Moreover, about 3% of the patients with critical disease carried biochemically validated IEIs, including both pLOF and in-frame variants. Remarkably, four adult patients had autosomal recessive IRF7 or IFNAR1 deficiency, providing compelling evidence that IEIs of type I interferon can underlie critical COVID-19. Additional patients with the same and related recessive deficiencies (e.g., TYK2, STAT2, TBK1) have since been reported (80–84). In a subsequent study, the initial findings were extended, with an enrichment of pLOF variants in the 13 influenza susceptibility genes and *TYK2* (85). Furthermore, a study of children with COVID-19 pneumonia found recessive IEIs in 10% of cases, including children with autosomal recessive TYK2 deficiency (82). These findings collectively incriminate type I interferons and suggest that TLR3 sensing of dsRNA in respiratory epithelial cells is essential for host defense against SARS-CoV-2. In at least fibroblasts and perhaps also in respiratory epithelial cells, TLR3 can sense viral intermediates or by-products, as well as unknown agonists that govern the basal, tonic levels of type I interferon (78, 86).

A genome-wide approach tested the hypothesis that rare nonsynonymous variants in specific genes may be enriched in patients with critical COVID-19 pneumonia, when compared with patients having silent or mild infection. No gene reached statistical significance on autosomes when a recessive model was considered. However, variants at the X-linked *TLR7* locus were enriched in male patients with critical COVID-19 pneumonia. The enrichment was stronger after all *TLR7* variants were tested biochemically, as none of the patients with silent or mild infection had TLR7 deficiency, and >1% of male patients with critical COVID-19 pneumonia had X-linked recessive TLR7 deficiency (81). Moreover, when reanalyzing untested TLR7 variants reported in other studies, we found that about half of them were biochemically deleterious, all of which were found in patients with hypoxemic pneumonia (81, 87, 88). Some TLR7-deficient relatives of index cases, however, did not develop hypoxemic pneumonia upon SARS-CoV-2 infection, implying that clinical penetrance is high but incomplete (81). Patients with X-linked recessive TLR7 deficiency were prone to critical COVID-19 because of impaired sensing of SARS-CoV-2 by pDCs. It had been previously shown that pDCs sense the virus via the UNC93B1- and IRAK-4-dependent pathway, suggesting that TLR7 and/or TLR9 upstream are essential (89). Unlike the case of respiratory epithelial cells, the virus does not replicate in pDCs. Their production of type I interferon in response to SARS-CoV-2 was abolished in patients with UNC93B1 or IRAK-4 deficiency. A recent study also showed that patients with IRAK-4 or MyD88 deficiencies are

highly vulnerable to severe or critical COVID-19 pneumonia (90). Additionally, we found that TLR7-deficient pDCs had a profoundly impaired but not entirely abolished production of type I interferon upon stimulation with SARS-CoV-2 (81).

Two cell types were therefore incriminated by different genetic approaches: respiratory epithelial cells because of IEIs of TLR3-dependent type I interferon immunity, and pDCs because of TLR7-dependent type I interferon immunity. It is worth noting that the genome-wide burden test itself, prior to any biochemical, immunological, and virological studies, incriminated pDCs (81). Indeed, TLR8 is also encoded on the X chromosome and expressed in endosomes, and both its agonists and pathway are shared with TLR7. The most striking difference is that TLR7 is expressed in pDCs, unlike TLR8. This genetic study indicated that host defense against at least SARS-CoV-2 requires not only TLR7 but also pDCs (81). This genome-wide study of critical COVID-19 also solved the conundrum of why IRAK-4-, MyD88-, and UNC93B1-deficient patients would not suffer from TLR7–9-related viral diseases, despite the three genes being under negative selection (81, 90). Our findings suggest that previous viral epidemics or pandemics related to SARS-CoV-2 have maintained TLR7 under negative selection. Viruses controlled by TLR8 or TLR9, if any, remain to be discovered. Another immunological implication of these studies is that human pDCs are essential for host defense against at least one virus. Their unique capacity to produce high levels of type I interferon, because of their constitutively high levels of IRF7 expression, suggested that pDCs contribute to antiviral immunity. Genetic evidence was, however, lacking in the absence of inherited selective defect of human pDCs. X-linked recessive TLR7 deficiency now provides strong evidence that human pDCs are essential for host defense against at least one virus.

Remarkably, both the candidate and the genome-wide approaches converged to incriminate type I interferon. The surprise, however, is not so much that IEI of type I interferon can underlie critical COVID-19 pneumonia but that these profound deficiencies can be silent for years or decades prior to SARS-CoV-2 infection. The patients with critical COVID-19 due to autosomal recessive IFNAR1, IRF7, STAT2, or TYK2 deficiency were healthy until the ages of 1.5 to 13 years. Patients with X-linked recessive TLR7 deficiency were also healthy until infected with SARS-CoV-2. These findings therefore suggested that human type I interferons (for IFNAR1-deficient patients), type I and III interferons other than IFN-β (for IRF7-deficient patients), ISGF-3-dependent type I and III interferons (for STAT2-deficient patients), TYK2-dependent cellular responses to type I interferons, and TLR7-dependent production of type I interferons were largely nonredundant for protective immunity against viruses. This was not surprising, as type I and III interferons are widely thought to be essential for host defense against most if not all viruses (91, 92). Earlier studies, however, suggested that type I interferons were redundant against many viruses (20, 46). It was even questioned whether type III interferons play any essential role in antiviral immunity, as IL-10RB-deficient patients, before or after hematopoietic stem cell transplantation, did not display any unusually severe viral disease (93). These were, however, reports of rare patients. An ascertainment bias was recently found to be unlikely, when null *IFNAR1* and *IFNAR2* alleles were found to be common in populations of Polynesian and Arctic origins, respectively (94–96). Children, adolescents, and adults without type I interferons can apparently control many viruses well, yet they display a high but selective vulnerability to a few viruses, including SARS-CoV-2, certain seasonal influenza viruses and by inference pandemic influenza viruses, and the attenuated live virus vaccine strains of measles-mumps-rubella (MMR) and by inference wild-type measles virus. The penetrance for these viral diseases even seems incomplete. The basis for this variable disease presentation, as well as that for normal resistance to many viruses in the absence of type I interferons, remains unexplained.

The above-described rare variant analyses were the first to identify genes important for type I interferon immunity as essential for protective immunity to SARS-CoV-2 in the respiratory tract.

These discoveries were also complemented by the identification of several common variants affecting the same pathway. Multiple genome-wide association studies (GWAS) of COVID-19 have been performed, using datasets from the GenOMICC (Genetics Of Mortality In Critical Care) cohort of initially 2,244 (later expanded to 7,491) critically ill UK patients, as well as from the COVID-19 Host Genetics Initiative (COVID-19 HGI) cohort of 49,562 SARS-CoV-2-infected patients (of all disease severities) across 19 countries (97–99). These studies identified approximately 30 different loci associated with susceptibility to COVID-19 (97–101). Some loci were located at or close to genes involved in host immune responses to virus infection, including type I interferon immunity. The association with the gene cluster including the ISGs *OAS1*, *OAS2*, and *OAS3* on chromosome 12q24.13, first identified in GenOMICC and COVID-19 HGI studies, was confirmed in additional patient cohorts of European and African ancestries (97, 99, 102–104). Two associated *OAS1* exonic variants (rs10774671 and rs1131454) were shown to regulate OAS1 protein levels through splicing and nonsense-mediated decay (102). Other interferon-related association loci that have been identified are *TYK2* on chromosome 19p13.2 (97, 99), *IFNAR2* on chromosome 21q22.1 (97, 99), and *IFNA10* on 9p21.3 (98). Since common variants have small or modest effect sizes, the ability of GWAS to detect other interferon-related loci may be highly sensitive to the population characteristics of cases and/or controls. Factors possibly obscuring signal detection include different ancestries/ethnic background, age, clinical severity definitions, etc. Indeed, age-stratified effects have been seen in some COVID-19 GWAS in which certain GWAS signals had significant stronger effect in the younger age group (<60 years) (98). Finally, as discussed earlier, given that SARS-CoV-2 is highly mutable, different variants of SARS-CoV-2 with different abilities to interfere with type I interferon immunity, including those arising within immunosuppressed individuals, may also confound ability to detect other interferon-related susceptibility loci.

PREEXISTING AUTOANTIBODIES NEUTRALIZING TYPE I INTERFERONS CAN UNDERLIE CRITICAL COVID-19

By analogy with autoantibodies to other cytokines resulting in clinical phenocopies of IEIs of the corresponding cytokines, the identification of patients with IEIs of type I interferons in 1–5% of cases raised the hypothesis that autoantibodies to type I interferons may underlie critical COVID-19 in other patients (105). This turned out to be correct and led to the discovery that >15% of patients suffer from critical COVID-19 because of autoantibodies neutralizing type I interferons (106–109). The natural occurrence of these autoantibodies had been described from the early 1980s onward in patients with systemic lupus erythematosus (SLE), thymoma, or myasthenia gravis. These autoantibodies were widely thought to be clinically silent, not being responsible for severe viral disease, with the notable exception of a patient with disseminated zoster studied by Ion Gresser (110). The autoantibodies found in patients with critical COVID-19 neutralize the 13 subtypes of IFN-α and/or IFN-ω, more rarely IFN-β. Neutralization of IFN-ε and IFN-κ, which are 1,000 times less potent and the expression of which predominates in reproductive and cutaneous tissues, has not been tested. About 10% of patients have autoantibodies that neutralize 10 ng/mL of interferon, with blood diluted 1/10, while another 5% neutralize 100-fold-lower concentrations. The risk of life-threatening disease increases with the number and concentration of type I interferons neutralized, with odds ratios varying between 5 and 100 (106). The autoantibodies were found in about 20% of deceased patients across age groups. They were also found to confer a high risk of death, with an infection fatality rate much greater than that conferred by sex, comorbidities, or the most significant at-risk haplotype detected by GWAS (108). Their impact was also documented in vivo during infection, both at the mucosal surface (111) and in leukocytes

EVIDENCE THAT AUTOANTIBODIES AGAINST TYPE I INTERFERONS CONFER SUSCEPTIBILITY TO LIFE-THREATENING COVID-19

Multiple lines of evidence support a pathogenic role of autoantibodies against type I interferons for worsened outcome of SARS-CoV-2 infections in humans. Definitive evidence in vivo awaits large-scale and better-designed prospective studies in humans, including interventional trials to deplete such autoantibodies. Adapted from Reference 108.

- The autoantibodies are detectable in patients, at times predating SARS-CoV-2 infection. In the general population, autoantibodies increase with age.
- The autoantibodies are more prevalent in patients with increased severity of SARS-CoV-2 infection, including those with certain autoimmune disorders associated with higher risk of severe SARS-CoV-2 infection.
- The autoantibodies neutralize type I interferon both in vitro and in vivo and thereby interfere with the ability to suppress SARS-CoV-2 replication.
- The autoantibodies phenocopy genetic defects in type I interferon immunity, as an additional example of anticytokine autoantibodies phenocopying their corresponding genetic defects in other cytokines.
- The autoantibodies can underlie susceptibility to other viral illnesses, such as severe influenza pneumonia and adverse reactions to the live attenuated yellow fever virus.

(112). These findings have since been replicated in various ways in at least 26 independent centers in the Americas, Asia, and Europe (112–137). Neutralization of high concentrations of multiple interferons was even found to account for 20% of cases of breakthrough hypoxemic pneumonia, in patients whose antibody response to the RNA vaccine was normal (138). Multiple lines of evidence indicate that these autoantibodies preexist infection with SARS-CoV-2 and are causal of critical disease (see the sidebar titled Evidence That Autoantibodies Against Type I Interferons Confer Susceptibility to Life-Threatening COVID-19) (108). Particularly relevant medically, these autoantibodies are found in the general population, with a prevalence that sharply rises after age 65 years, reaching 5–8% in the elderly population (106).

In a subset of patients studied longitudinally, levels of neutralizing anti-type I interferon autoantibodies appeared highest during acute SARS-CoV-2 infection and then decreased during convalescence, although most patients maintained some neutralizing activity several months out (139). In a complementary study that included two COVID-19 patients with preexisting neutralizing anti-type I interferon autoantibodies, acute SARS-CoV-2 infection caused a transient increase in the amount of these autoantibodies (140). Since the presence of these autoantibodies, even during acute COVID-19, is associated with a dramatically increased likelihood of developing severe or critical outcomes, these kinetic data suggest that a small memory B cell population exists in some individuals that can rapidly expand and differentiate into plasmablasts upon antigenic type I interferon exposure or because of bystander activation, which has been shown to be precipitated by viral infection (105). Indeed, multiple autoantibodies have been detected in patients with COVID-19 or other infections (125). Such a situation might be more likely to occur upon infection with a virulent virus to which the individual is immunologically naive, i.e., a situation in which there is widespread viral replication and type I interferon induction. This could explain why patients with neutralizing anti-type I interferon autoantibodies tend to be older, as they might require repeated and prolonged exposure in the past to type I interferons to break tolerance. Furthermore, this requirement may also explain why patients with these autoantibodies do not generally have a history of life-threatening infections by other viruses. This model raises the alarming possibility that

severe or protracted COVID-19 might be a factor predisposing to future severe viral infections in individuals who already have neutralizing anti-type I interferon autoantibodies.

These findings also raise various questions pertaining to the origin, nature, and consequences of autoantibodies to type I interferons. Their origin is unknown in most cases, especially in the significant proportion of elderly people who carry them. Known associations include SLE, thymoma, and myasthenia gravis, conditions that were long known to be associated with these autoantibodies. Autoantibodies to type I interferons have also been more recently described in incontinentia pigmenti (IP) (107); partial deficiencies of RAG1/2 (141); immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) (142), and autoimmune polyendocrinopathy syndrome type I (APS-1; also known as APECED) (143). The latter condition is particularly important, because most if not all patients with APS-1 display such autoantibodies from early childhood onward. These observations in patients hint that tolerance to type I interferons may be broken through a mechanism involving failure to delete autoreactive T cells that promote B cell type I interferon autoantibody production. So far, all known IEIs underlying autoantibodies to type I interferons involve defective thymopoiesis, whether due to a T cell–intrinsic defect (mutations in *RAG1*, *RAG2*, and *FOXP3*) or a medullary thymic epithelial cell–intrinsic defect (mutations in *AIRE*). Moreover, the occurrence of autoantibodies to type I interferons in thymoma is probably explained by the localized defect of expression of AIRE within the lesion (144). These findings raise the exciting possibilities that a not negligible proportion of patients with various other autoimmune conditions carry autoantibodies to type I interferons predisposing them to critical COVID-19 and that they could be considered to have occult IEIs.

The nature of these autoantibodies is also largely elusive. What are the components of the heavy and light chains of the antibodies, and the corresponding B cell epitopes? Is there an HLA association, and what are the corresponding T cell epitopes? What are the frequencies of type I interferon–specific T and B cells in the blood? What are the differences between autoantibodies recognizing IFN-α, IFN-ω, and IFN-β? Finally, the consequences of these autoantibodies need to be unraveled. They were already shown to account for about a third of a small cohort of patients with adverse reaction to the live attenuated yellow fever virus vaccine (145). They are also found in about 5% of patients under 70 years old with severe influenza pneumonia (146). Finally, and consistent with Ion Gresser's seminal report, they were found to be associated with recurrence of varicella-zoster virus flares in patients hospitalized with COVID-19 (110, 115). Longitudinal studies of people with autoantibodies to type I interferons are warranted to delineate their natural history of viral resistance and susceptibility.

EFFECTS OF ACTIVATING THE TYPE I INTERFERON PATHWAY APPEAR BENEFICIAL EARLY BUT NOT LATER DURING SARS-CoV-2 INFECTIONS IN HUMANS

While deficiency of type I interferon in humans, either through loss-of-function gene mutations or neutralizing anticytokine autoantibodies, predisposes to life-threatening COVID-19, it remains an open question whether increased or prolonged production of type I interferon during SARS-CoV-2 infection can in some circumstances contribute to severe disease through different mechanisms. Constitutive overproduction of type I interferon in humans occurs in a group of disorders called type I interferonopathies, which often result from mutations in genes involved in nucleic acid metabolism or sensing (27). Interferonopathies as a group characteristically manifest autoinflammatory and sometimes autoimmune disease. Most patients have central nervous system involvement including intracranial calcification and skin disease including pernio, but some can also develop pulmonary, ocular, or gastrointestinal involvement. Remarkably though,

these patients do not apparently have increased susceptibility to life-threatening SARS-CoV-2 infections. Instead, they might be better protected from developing severe disease because their increased basal production of type I interferon keeps their cells in an antiviral state. This idea is supported by a recent study in which the differentiated macrophage cell line THP-1 was rendered SAMHD1-deficient by knockout, to mimic one cause of inherited type I interferonopathy (147). Such cells showed decreased SARS-CoV-2 transcripts after infection, along with the expected biochemical markers of increased type I interferon signaling. Primary human monocyte-derived macrophages in which SAMHD1 was targeted for degradation by treatment with Vpx-containing virus-like particles also showed similarly decreased SARS-CoV-2 transcripts after infection.

Consistent with the idea that the early increase in type I interferon is protective rather than deleterious, a subgroup of patients develop chilblain-like lesions (pernio) after exposure to SARS-CoV-2. These young individuals develop pernio on their extremities (so-called COVID toes), but most report no extracutaneous symptoms of COVID-19 (148). Infection with SARS-CoV-2 was inferred by epidemiological exposure histories, although only a minority of these patients have serological evidence of prior infection, and most test negative by conventional PCR at the onset of pernio. Early histopathologic studies demonstrated SARS-CoV-2 proteins in endothelial cells and eccrine gland epithelial cells (149). However, those findings were not replicated in a subsequent study, suggesting that an abortive SARS-CoV-2 infection might have occurred, resulting in very low, barely detectable levels of virus (150). Intriguingly, when peripheral blood mononuclear cells (PBMCs) from these individuals were stimulated in vitro by a TLR7/8 ligand, type I interferon production was increased compared with PBMCs from individuals with acute respiratory COVID-19 (mild or severe) (149), and pDCs present within affected tissue have been implicated in the pathogenesis of other forms of pernio (151, 152). Moreover, increased expression of ISGs ex vivo was observed not only in skin but also in blood of patients with COVID-19-associated or other forms of pernio, when compared to healthy controls or COVID-19 patients with mild respiratory symptoms (152). Since TLR7 and pDCs are important for protection against acute respiratory COVID-19 (see above) (81), it seems plausible that a hyperactive type I interferon response elicited early upon SARS-CoV-2 exposure makes it difficult to detect residual virus products later in COVID-19-associated pernio patients. Other post-COVID-19 sequelae like what is seen in type I interferonopathies have been anecdotally reported, such as myopathy and dermatomyositis (153, 154). Overall, these observations suggest a common protective mechanism involving increased early type I interferon similar to what is seen in type I interferonopathies.

As genetic or acquired type I interferon deficiency is associated with more severe COVID-19, several randomized clinical trials have been carried out to test efficacy of type I interferon administration. The trials have used IFN-β, which fortuitously is less likely to be neutralized by endogenously arising autoantibodies (see the above section titled Preexisting Autoantibodies Neutralizing Type I Interferons Can Underlie Critical COVID-19). Depending upon the timing of type I interferon treatment relative to onset of symptoms and severity of disease when treatment was started, these trials could provide clues regarding possible deleterious effects of delayed exposure to type I interferon. However, clinical trials are difficult to control given many potential confounding factors such as age, sex, severity, comorbid conditions, and other treatments, not to mention the uniqueness of the genome of each participant. Stratification and subgroup analyses are typically used to take these factors into account, but even so overall the trials have yielded mixed results.

An early randomized open-label trial by Hung et al. (155) compared (*a*) a 14-day treatment course of subcutaneously administered nonglycosylated IFN-β ($n = 86$) combined with ribavirin and lopinavir-ritonavir with (*b*) lopinavir-ritonavir only. Treatment was started at no more than 7 days after symptom onset [median 5 days, interquartile range (IQR) 3 to 5 days] in a hospitalized

patient cohort that tended to have milder disease. In the group additionally treated with IFN-β and ribavirin, there was more rapid clearance of SARS-CoV-2 PCR positivity from the upper respiratory tract, as well as more rapid resolution of clinical symptoms and organ dysfunction (155). In a randomized, double-blind, placebo-controlled trial by Monk et al. (156), a 14-day treatment course of nebulized glycosylated IFN-β ($n = 48$) was started at a median of 10 days after symptom onset (IQR 7 to 11 days). Here, the IFN-β-treated group showed a greater likelihood of clinical improvement and quicker recovery compared with placebo control, despite having an initially worse baseline severity score before treatment. The IFN-β treatment appeared well-tolerated, with only headache and cough during aerosolized administration, as previously observed when it was administered in other clinical conditions such as asthma, and there were no deaths in the IFN-β-treated group. Thus, these two studies suggested that treatment with type I interferon can be efficacious.

Two other randomized open-label trials at a single center tested a 14-day treatment course of different forms of IFN-β added onto a regimen of hydroxychloroquine plus lopinavir-ritonavir (or atazanavir-ritonavir) in more severely ill hospitalized patients (157, 158). Treatment was started at a median of 10 days (IQR 8 to 13 days) after symptom onset for glycosylated IFN-β or 7 days (IQR 5 to 9 days) for nonglycosylated IFN-β. In those who had received additional subcutaneously injected glycosylated IFN-β ($n = 42$) earlier (defined as <10 days after symptom onset), time to resolution of symptoms was not decreased, but the proportion of those discharged from the hospital at 14 days was increased and 28-day mortality was decreased, effects that were reported as not seen in patients who started receiving type I interferon later (157). For the parallel study of nonglycosylated IFN-β ($n = 33$), the proportion of patients discharged from the hospital at 14 days was also increased, but there were several differences including decreased time for resolution of symptoms and unaffected 28-day mortality (158). Of note, in the study of glycosylated IFN-β, several patients were censored from the treatment group because they died before receiving at least four doses of IFN-β (157). It is unclear whether these deaths occurred in individuals who started to receive IFN-β earlier or later, and whether these deaths reflect a deleterious effect of delayed interferon administration.

On the other hand, several open-label randomized clinical trials did not show any clear benefit of IFN-β administration. In a study by the WHO Solidarity Trial Consortium, a 7-day course of glycosylated IFN-β ($n = 2{,}050$), sometimes combined with lopinavir, in hospitalized patients with COVID-19 of at least moderate severity did not decrease mortality, respiratory support, or duration of hospitalization, although there did appear to be a non–statistically significant increased likelihood of death in those who were ventilated (159). However, some critically ill patients received intravenous IFN-β along with corticosteroids, instead of subcutaneous IFN-β, complicating the interpretation. Furthermore, the duration of symptoms prior to treatment was not provided, so whether the timing of administration of IFN-β affected outcome is unknown. Similarly, in a randomized open-label trial from Ader et al. (160), a 7-day course of glycosylated IFN-β ($n = 145$) was given along with lopinavir-ritonavir to hospitalized patients with COVID-19 of moderate or greater severity and a median symptom duration since onset of 10 days (IQR 7 to 12 days). Treatment did not improve clinical score, decrease time to hospital discharge, or result in more rapid clearance of virus from the respiratory tract.

Further complicating the picture, a double-blind, placebo-controlled trial has tested effects of glycosylated IFN-β in sicker hospitalized patients. In the ACTT-3 trial, a 7-day treatment course of subcutaneously administered IFN-β ($n = 477$) was given in combination with the antiviral remdesivir, with treatment starting at a median of 8.7 days (standard deviation 4.4 days) after symptom onset (161). Even when analysis was adjusted for actual disease severity, treatment with IFN-β plus remdesivir in those who were moderately or severely ill did not result in quicker

recovery compared to remdesivir alone. Furthermore, those who were critically ill also had higher likelihood of clinically worsening with the additional IFN-β treatment. Interpretation of these results is difficult since unlike lopinavir-ritonavir or hydroxychloroquine (which have since been shown not to be beneficial for clinical outcome in SARS-CoV-2-infected patients), remdesivir seems to have efficacy to prevent severe illness when patients already require a low level of oxygen supplementation. Thus, in the ACTT-3 trial the lack of an effect of added IFN-β may be due to the beneficial effects of concurrently administered remdesivir (162).

In summary, it appears that situations of increased type I interferon produced endogenously, either at baseline before infection (type I interferonopathies) or early during the course of natural infection (pernio), are associated with less severe clinical disease. This is consistent with an early protective effect of type I interferon. By contrast, when type I interferon is provided exogenously in interventional clinical trials, it is started several days after initial symptoms develop, when it is probably too late to see beneficial clinical effects, especially in more severely affected patients (109, 163). This essentially delayed provision of type I interferon is not protective, and there are hints that it might worsen clinical outcomes, but more evidence in humans is needed to support such a conclusion. Testing the therapeutic effect of type I interferon in asymptomatic, ambulatory, unvaccinated individuals, shortly after a diagnosis of SARS-CoV-2 infection but before they become patients, would be highly informative. If efficacious, it would not only provide a new preventive therapy but also further incriminate inadequate type I interferon in the first days of infection as a general mechanism of disease.

AGE AND CRITICAL COVID-19: FACTS AND HYPOTHESES

During the pandemic, age has emerged as the most important epidemiological determinant for clinical outcome to SARS-CoV-2 infection. At the molecular and cellular levels, age-dependent factors contributing to outcome could include physiological differences such as different patterns of alveolar ACE2 expression and different numbers of lung progenitor cells in children versus older adults (164). Our discovery that defects in the type I interferon pathway are a strong determinant for poor outcome also raises the possibility that SARS-CoV-2-elicited induction of type I interferons and cellular responses to them may themselves vary with age. As we have shown, the prevalence of autoantibodies neutralizing type I interferon is stable, between 0.3% to 1%, until age 65 years, and then it rises sharply to reach 4–8% (106). Additional contributing factors could include declines with age in pDC counts and basal levels of type I interferon in respiratory mucosae that have been observed in other contexts (165, 166). We speculate that the overall decline of type I interferon immunity with age accounts, at least in part, for the epidemiological observation of age-dependent COVID-19 mortality. The molecular and cellular bases of this decline remain, however, largely unknown. Future research into this important topic may shed light into the age-dependent susceptibility that is observed with other viral infections.

CONCLUSIONS

In this review, we have focused on the mechanisms of life-threatening COVID-19 pneumonia in humans. We now know that inborn errors of TLR3- or TLR7-dependent type I interferon immunity occur in about 1–5% of patients with hypoxemic COVID-19 pneumonia, with the penetrance of recessive defects higher than that of dominant defects. We also know that preexisting autoantibodies neutralizing IFN-α, IFN-β, and/or IFN-ω occur in about 15–20% of patients with hypoxemic pneumonia. These autoantibodies are found in 0.3–1% of healthy individuals until age 65 years, when their prevalence sharply increases to reach up to 4–7% above 75 years old. In a small proportion of cases, these autoantibodies appear driven by inborn errors of T cell tolerance

in the thymus. Collectively, these findings suggest that insufficient type I interferon, whether inherited or acquired, might be a general mechanism of hypoxemic COVID-19 pneumonia. Many unknowns remain. Are there other pathogenic inborn errors of type I interferon, especially affecting type I interferon–inducible genes that could alter cellular responses to type I interferons? Are there other inborn errors of thymopoiesis underlying autoantibodies to type I interferons? Why does their prevalence increase sharply above 65 years of age? Finally, is type I interferon deficiency the only mechanism at work in patients, or do other mechanisms contribute to life-threatening COVID-19 pneumonia, such as proinflammatory/immunomodulatory effects of inappropriately high or misdirected type I interferon?

DISCLOSURE STATEMENT

J.-L.C. is an inventor on patent application PCT/US2021/042741, filed July 22, 2021, submitted by The Rockefeller University that covers diagnosis of, susceptibility to, and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. S.E.H. is an ad hoc member of the Advisory Board of Horizon Therapeutics. V.S. is a full-time employee at Owkin. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

Huie Jing drafted the outline and wrote the corresponding section titled Type I Interferons and Their Functions and prepared **Figure 2**.

Helen C. Su wrote the abstract; drafted the outline and wrote the corresponding sections titled (*a*) SARS-CoV-2-Encoded Proteins Antagonize the Host Type I Interferon Antiviral Response, (*b*) Mouse Models of SARS-CoV-2 Infection: Variable Impacts of Type I Interferon on Disease Outcome, and (*c*) Effects of Activating the Type I Interferon Pathway Appear Beneficial Early but Not Later During SARS-CoV-2 Infections in Humans; and prepared **Figure 1** and the sidebar titled Evidence That Autoantibodies Against Type I Interferons Confer Susceptibility to Life-Threatening COVID-19.

Jean-Laurent Casanova drafted the outline and wrote the sections titled (*a*) COVID-19, (*b*) Age and Critical COVID-19: Facts and Hypotheses, and (*c*) Conclusions.

The section titled Genetic Lesions Affecting the Type I Interferon Pathway in Humans had its outline codrafted/cowritten by Jean-Laurent Casanova, Yu Zhang, and Helen Su.

The section titled Preexisting Autoantibodies Neutralizing Type I Interferons Can Underlie Critical COVID-19 had its outline codrafted/cowritten by Jean-Laurent Casanova and Helen Su.

Members of the COVID Human Genetic Effort who were included in this coauthorship list contributed to biweekly discussion of concepts developed in this review for all the sections, identified relevant citations for inclusion, and revised the review critically for important intellectual content: Laurent Abel, Alessandro Aiuti, Saleh Al-Muhsen, Mark S. Anderson, Evangelos Andreakos, Andrés A. Arias, Lisa M. Arkin, Paul Bastard, Vivien Béziat, Bertrand Boisson, Stephanie Boisson-Dupuis, Alexandre Bolze, Ahmed A. Bousfiha, Jacinta Bustamante, Jean-Laurent Casanova, John Christodoulou, Aurélie Cobat, Roger Colobran, Antonio Condino-Neto, Jacques Fellay, Carlos Flores, José Luis Franco, Guy Gorochov, Rabih Halwani, Sarah E. Henrickson, Elena W.Y. Hsieh, Yuval Itan, Emmanuelle Jouanguy, Elżbieta Kaja, Yu-Lung Lau, Davood Mansouri, Isabelle Meyts, Kristina Mironska, Trine H. Mogensen, Lisa F.P. Ng, Cliona O'Farrelly, Satoshi Okada, Rebeca Perez de Diego, Jordi Perez-Tur, David S. Perlin, Anne Puel, Lluis Quintana-Murci, Laurent Renia, Carlos Rodríguez-Gallego, Anna Sediva, Mikko R.J. Seppänen, Anna Shcherbina, Andrew L. Snow, Pere Soler-Palacín, Vassili Soumelis, András N. Spaan, Helen

C. Su, Ivan Tancevski, Stuart G. Tangye, Ahmad Abou Tayoun, Şehime Gülsün Temel, Christian Thorball, Pierre Tiberghien, Stuart E. Turvey, K.M. Furkan Uddin, Qian Zhang, and Shen-Ying Zhang.

ACKNOWLEDGMENTS

This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) (H.C.S., H.J., Y.Z.). The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute; The Rockefeller University; the St. Giles Foundation; the NIH (R01AI088364, R01AI163029, and R21AI160576); the National Center for Advancing Translational Sciences (NCATS); the NIH Clinical and Translational Science Award (CTSA) program (UL1TR001866); the Yale Center for Mendelian Genomics and the GSP Coordinating Center, funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956); the Yale High Performance Computing Center (S10OD018521); the Fisher Center for Alzheimer's Research Foundation; the Meyer Foundation; the JBP Foundation; the French National Research Agency (ANR) under the "Investments for the Future" program (ANR-10-IAHU-01); the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID); the French Foundation for Medical Research (FRM) (EQU201903007798); the ANRS-COV05, ANR GENVIR (ANR-20-CE93-003), ANR GenMISC (ANR-21-COVR-039), and ANR AABIFNCOV (ANR-20-CO11–0001) projects; the European Union's Horizon 2020 research and innovation program under grant agreement number 824110 (EASI-genomics); the HORIZON-HLTH-2021-DISEASE-04 program under grant agreement 01057100 (UNDINE); the ANR-RHU Program ANR-21-RHUS-08 (COVIFERON); the Square Foundation; Grandir—Fonds de Solidarité pour l'Enfance; the Fondation du Souffle; the SCOR Corporate Foundation for Science; the French Ministry of Higher Education, Research, and Innovation (MESRI-COVID-19); and Institut National de la Santé et de la Recherche Médicale (INSERM) and the University of Paris Cité (J.-L.C.). We thank Dana Liu for clerical assistance. This review is dedicated to the memory of Christine Biron.

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