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Review article

Inherited and acquired errors of type I interferon immunity govern susceptibility to COVID-19 and multisystem inflammatory syndrome in children

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Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) pandemic, global sequencing efforts have led in the field of inborn errors of immunity, and inspired particularly by previous research on life-threatening influenza, they have revealed that known and novel inborn errors affecting type I interferon immunity underlie critical COVID-19 in up to 5% of cases. In addition, neutralizing autoantibodies against type I interferons have been identified in up to 20% of patients with critical COVID-19 who are older than 80 years and 20% of fatal cases, with a higher prevalence in men and individuals older than 70 years. Also, inborn errors impairing regulation of type I interferon responses and RNA degradation have been found as causes of multisystem inflammatory syndrome in children, a life-threatening hyperinflammatory condition complicating otherwise mild initial SARS-CoV-2 infection in children and young adults. Better understanding of these immunologic mechanisms can aid in designing treatments for severe COVID-19, multisystem inflammatory syndrome in children, long COVID, and neuro-COVID. (J Allergy Clin Immunol 2023;151:832-40.)

Key words: *COVID-19, SARS-CoV-2, multisystem inflammatory syndrome in children, type I interferon*

In December 2019, the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a novel human pathogen causing coronavirus 2019 disease (COVID-19), an infection characterized by pneumonia and acute respiratory failure in a significant proportion of cases (5%-15%).[1-3] Like other respiratory viruses, SARS-CoV-2 enters and infects respiratory epithelial cells, mostly by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, where it replicates. It can then spread to other organs, mainly through a viremic phase. The detection of viral components through pattern recognition receptors (including Toll-like receptors [TLRs], retinoic acid–inducible gene I [RIG-I]-like receptors, and nucleotide-binding oligomerization domain [NOD]-like receptors [NLRs]) and cytosolic sensors (such as cyclic guanosine monophosphate–AMP synthase), activates an antiviral response in infected epithelial cells as well as in leukocytes governing the innate immune response, such as macrophages, monocytes, dendritic cells, neutrophils, and innate lymphoid cells.[4,5] Type I and type III interferon signal through the interferon receptors (IFNAR1/2 for type I interferon and IFNLR1/IL10RB for type III interferon) and signal transducer and activator of transcription (STAT) 1 and 2, which combine with interferon regulatory factor 9 (IRF9) to induce the expression of interferon-stimulated genes responsible for antiviral defense. The interferon response needs to be finely tuned to strike a balance between virus clearance and prevention of excessive inflammation, which can be further exacerbated by the viral-induced activation of the inflammasome and cause a cytokine storm mediated by inflammatory cell death.[5]

From the start of the pandemic, around 0.5% to 1% of patients died and 2% to 4% experienced critical disease globally.[6,7] Risk factors for critical COVID-19 are age (with a doubling of the risk every 5 years of age), male sex, and comorbidities such as obesity, type 2 diabetes, and chronic lung disease.[7,8] However, the impact of the comorbidities in terms of odds ratio is at best limited and does not explain the striking interindividual variability in severity of disease following SARS-CoV-2 infection. In an attempt to explain this variability, several international consortia have searched for rare or common human genetic variants on a large scale that could modify the risk of infection or of severe

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Abbreviations used

ACE2: Angiotensin-converting enzyme 2
APS1: Autoimmune polyendocrinopathy syndrome 1
CGD: Chronic granulomatous disease
COVID-19: Coronavirus disease 2019
CYBB: Cytochrome B-245 β-chain
dsRNA: Double-stranded RNA
HLH: Hemophagocytic lymphohistiocytosis
IFNAR1/2: IFN-α receptor1/2
IFNLR1: IFN-λ receptor 1
IL-10RB: IL-10 receptor β
IRF9: Interferon regulatory factor 9
MAVS: Mitochondrial antiviral signaling
MIS-C: Multisystem inflammatory syndrome in children
MYD88: Myeloid differentiation factor 88
NADPH: Nicotinamide adenine dinucleotide phosphate
NLR: NOD-like receptor
OAS: 2'-5'-Oligoadenylate synthetase
RIG-I: Retinoic acid-inducible gene I
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
STAT: Signal transducer and activator of transcription
SOCS1: Suppressor of cytokine signaling 1
TLR: Toll-like receptor
XIAP: X-linked inhibitor of apoptosis

COVID-19.[9-14] In particular the COVID Human Genetic Effort (www.COVIDHGE.com) has made landmark discoveries to explain critical COVID-19. Consequently, a better understanding of the key players in human defense against SARS-CoV-2 led to the finding of other, acquired, immunologic risk factors. Finally, research has also concentrated on puzzling complications of COVID-19, such as multisystem inflammatory disease in children (MIS-C), long COVID, and "COVID toes." Here, we review the findings that have cast light on defects of innate immunity causing susceptibility to COVID-19 and MIS-C (summarized in Tables I-III[14-36] and Fig 1). The implication of these findings on the implementation of targeted treatment in patients with inborn errors of immunity or their phenocopies is beyond the scope of this review, and we refer readers to a previous review on this topic.[37]

MONOGENIC TYPE I INTERFERON DEFECTS AND SEVERE COVID-19

The initial focus of the COVID Human Genetic Effort was centered on inborn errors of type I interferon immunity in patients with life-threatening COVID-19.[15,27,38,39] SARS-CoV-2 and influenza are both RNA viruses affecting the respiratory tract and causing life-threatening pneumonia. Thus, it was hypothesized that predisposition to critical COVID-19 and influenza could be allelic. Zhang et al therefore analyzed 3 genetic loci underlying influenza susceptibility (*TLR3*, *IRF7,* and *IRF9*) and 10 additional closely related loci involved in antiviral responses (*TRIF*, *TRAF3*, *TBK1*, *UNC93B1*, *IRF3*, *STAT1*, *STAT2*, *IFNAR1*, *IFNAR2*, and *NEMO*) in 659 patients of all ages with critical COVID-19 and a control group of 534 individuals with mild or asymptomatic COVID-19.[15] They found an enrichment in monoallelic and biallelic pathogenic variants in 8 genes (*TLR3*, *UNC93B1*, *TRIF*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, and *IFNAR2*) in the patients but not in the control group. A defect of TLR3- and IRF7-dependent type I interferon immunity was demonstrated in cells with complete IRF7 and IFNAR1 deficiency, as were an impaired intracellular response to infection with SARS-CoV-2 *in vitro* and significantly lower serum type I interferon levels *in vivo*.[15] These findings were confirmed by several additional reports of autosomal recessive IRF7, IFNAR1, TBK1, and TYK2 deficiency in patients with critical COVID pneumonia, including in children.[16,18-20,25]

Subsequently, the hypothesis that an enrichment of deleterious variants in the X chromosome could explain the higher proportion of males affected by severe COVID-19 was tested by using an unbiased approach.[21] This led to the discovery of X-linked recessive TLR7 deficiency in about 2% of males with critical COVID-19 pneumonia, including children.[20-23] The penetrance of severe SARS-CoV-2 infection appears to be high, but not complete, for the described recessive defects and lower for dominant defects. Interestingly, patients with autosomal recessive IFNAR1 or IRF7 deficiency had not previously developed severe disease following live viral vaccine administration, influenza virus infection, or other viral infections,[40-45] as has been described for earlier cases of individuals with pathogenic biallelic variants in these genes. This observation illustrates the variable expression of the phenotype as well as the redundancy of type I interferon responses for human defense against most viruses. Finally, some cases of critical SARS-CoV-2 pneumonia in patients with myeloid differentiation factor 88 (MyD88) or IRAK4 deficiency have also been reported.[26,46,47] MyD88 and IRAK4 are essential mediators of signaling downstream from TLR7, and a role for MyD88 in controlling pulmonary replication of SARS-CoV-1 in mice was previously shown.[48] Also, impaired type I/III interferon production following SARS-CoV-2 infection was shown *in vitro* in plasmacytoid dendritic cells from a patient with IRAK4 deficiency.[49]

The relevance of interferon-mediated immunity in the context of COVID-19 has also been confirmed by the findings of several population-based genome-wide association studies. For example, a recent genome-wide gene-based rare variant association analysis confirmed enrichment in rare loss-of-function variants in *TLR7*, *TYK2*, and several IRF7- and TLR3-dependent type I interferon immunity loci[50]; in addition, other genome wide association studies have demonstrated significant association of critical infection with variants involved in interferon signaling (*IFNAR2, TYK2, CCR2,* and *IL10RB*) and cytosolic double-stranded RNA (dsRNA) sensing (2'-5'-oligoadenylate synthetase 1 gene [*OAS1*], *OAS2,* and *OAS3*).[11,51] Other significant effects were found for loci related to the blood group and within the 3p21.31 region (possibly affecting ACE2 expression) regarding susceptibility to infection with SARS-CoV-2, and several loci related to lung disease regarding risk of severe infection.[10,11]

AUTOIMMUNE PHENOCOPIES OF TYPE I INTERFERON DEFECTS

Monogenic defects of antiviral immunity explain only a minor proportion of the patients with critical COVID-19 in the population younger than 60 years (estimated as 1%-5%).[52] The hypothesis that the presence of serum neutralizing autoantibodies against type I interferons could mimic these inborn errors in a larger proportion of severely affected patients was then raised. This phenocopy mechanism is well known in the field of immunodeficiencies. Indeed, autoimmune phenocopies of mendelian susceptibility to mycobacterial disease, invasive pneumococcal

TABLE I. Inborn errors of type I interferon immunity underlying susceptibility to severe COVID pneumonia

Gene	Inheritance	Other known phenotypes	Reference(s)
IRF7	AR	Influenza pneumonia	15-17
	AD	NA	
IFNAR1	AR	Fatal susceptibility to live viral vaccines, HLH	15,18-20
	AD	NA	
TLR7	XLR	NA	20-23
TLR3	AD	Influenza pneumonia, herpes simplex encephalitis	15,24
UNC93B1	AD	NA (AR herpes simplex encephalitis)	15
TICAM1	AD	Herpes simplex encephalitis	15
TBK1	AD	Herpes simplex encephalitis	15,25
IRF3	AD	Herpes simplex encephalitis	15
IFNAR2	AD	NA (AR fatal susceptibility to live viral vaccines)	15
STAT2	AR	Influenza pneumonia, fatal susceptibility to live viral vaccines, HLH	20
TYK2	AR	Susceptibility to mycobacteria and viruses, hyper-IgE syndrome	20
MYD88 and *IRAK4*	AR	Pyogenic infections	26, 47

Mechanism is disruption of an essential mediator of type I interferon responses. Proportion of severe COVID pneumonia in young patients (<60 years) explained in 1% to 5% of cases.

AD, Autosomal dominant; *AR*, autosomal recessive; *NA*, not applicable; *XLR*, X-linked recessive.

TABLE II. Autoimmune phenocopies of type I interferon defects underlying susceptibility to severe COVID pneumonia

Phenocopies of type I interferon defects	Reference(s)
Patients treated with recombinant IFN-α or IFN-β	27-33
Patients with autoimmune conditions:	
● SLE, myasthenia gravis, thymoma	
● Autoimmune polyendocrinopathy syndrome 1 (APS1, *AIRE* mutations)	
● Immune dysregulation, polyendocrinopathy, enteropathy, XL (IPEX, *FOXP3* mutations)	
● *RAG1*/*RAG2* hypomorphic mutations	
Circulating auto-Abs in otherwise healthy individuals, mostly men and those older than 65 y	

Mechanism is neutralizing autoantibodies against type I IFN. Proportion of critical COVID pneumonia is explained in 15% to 20% of cases.

IPEX, Immunodysregulation polyendocrinopathy enteropathy X-linked; *SLE*, systemic lupus erythematosus; *XL*, X-linked.

disease, and chronic mucocutaneous candidiasis have been attributed to neutralizing autoantibodies against the cytokines IFN-γ, IL-6, and IL-17A/F, respectively.[53-57] The presence of autoantibodies against type I interferon in patients with a variety of conditions, inborn and acquired, has been known for several decades. These include patients with elevated levels of type I interferon, such as those receiving therapy with IFN-α or IFN-β for multiple sclerosis or patients with SLE, patients with broad autoimmune diseases (such as thymoma and myasthenia gravis), and patients with immune defects of central or peripheral tolerance (such as autoimmune polyendocrinopathy syndrome 1, combined immunodeficiency with autoimmunity due to mutations in *RAG1* or *RAG2,* and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome).[58-64]

The clinical relevance of anti–type I interferon autoantibodies was unclear for several decades, and no association with viral infections was reported, except in a patient with varicella-zoster and some patients with RAG1 or RAG2 deficiency and severe chickenpox.[60,65,66] Indeed, although the presence of anti–type I interferon autoantibodies was being utilized as a diagnostic criterion for autoimmune polyendocrinopathy syndrome 1 (APS-1) and an inverse correlation between high titers of these antibodies and type 1 diabetes had been described, a clinical correlate for increased susceptibility for infection was lacking.[67] At the beginning of the pandemic, an early report illustrated the critical course of COVID-19 pneumonia in an Italian patient with APS-1.[68] Bastard et al then tested the hypothesis that autoantibodies against type I interferons could underlie severe COVID-19 and initially found that at least 10% of patients of all ages with critical pneumonia had neutralizing autoantibodies against IFN-α, IFN-ω, or both and that the rate of severe or critical pneumonia increased to 86% in patients with APS-1 with these neutralizing antibodies.[27,28] The study group also confirmed that this resulted in low or undetectable serum IFN-α levels during acute SARS-CoV-2 infection in all patients.[27] Strikingly, 94% of these patients were men, which could contribute to the higher prevalence of severe COVID-19 in males.[27]

The association of neutralizing autoantibodies against type I interferons and critical COVID-19 was confirmed by many independent studies.[28,29,69-76] It was shown that neutralizing autoantibodies against IFN-α or IFN-ω are rare in the general population (they are present in less than 1% of those between 20 and 70 years old), that their prevalence increases with age (reaching 4% of individuals older than 70 years), and that they are present in about 20% of both patients with critical COVID-19 who are older than 80 years and individuals with fatal cases in all age groups.[28,29,69-76] The presence of neutralizing anti–type I interferon autoantibodies correlates with an increased risk of death and an increased infection fatality rate in patients infected with SARS-CoV-2, and this risk rises with age.[30] This effect is seen both in the general population of patients with COVID-19 and in patients with APS-1, who showed a significantly higher risk of critical and fatal disease than did age-matched patients without the condition.[28] Moreover, in a cohort of 48 patients with breakthrough severe COVID-19 pneumonia after 2 doses of an mRNA vaccine, 24% of subjects had autoantibodies neutralizing type I interferons.[31] The presence of neutralizing anti–type I interferon autoantibodies could therefore explain the atypically severe infections in vaccinated individuals in at least a quarter of cases.[31] A role for anti–type I interferon autoantibodies in other severe viral diseases is being explored further, as these autoantibodies seem to be correlated with severe herpesvirus infections (eg, severe cutaneous herpes zoster, varicella pneumonia, varicella

TABLE III. Inborn errors of immunity underlying susceptibility to MIS-C

Gene	Inheritance	Other known phenotypes	Reference(s)
XIAP	XL	Familial HLH	34
CYBB	XL	Chronic granulomatous disease	14,34
SOCS1	AD	Early-onset familial autoimmunity	34,35
OAS1	AR	NA	36
OAS2	AR	NA	36
RNASEL	AR	NA	36

Mechanism is excessive inflammatory responses to SARS-CoV-2 due to defective viral RNA degradation and/or dysregulated interferon and inflammasome activation.
AD, Autosomal dominant; *AR*, autosomal recessive; *NA*, not applicable; *XL*, X-linked.

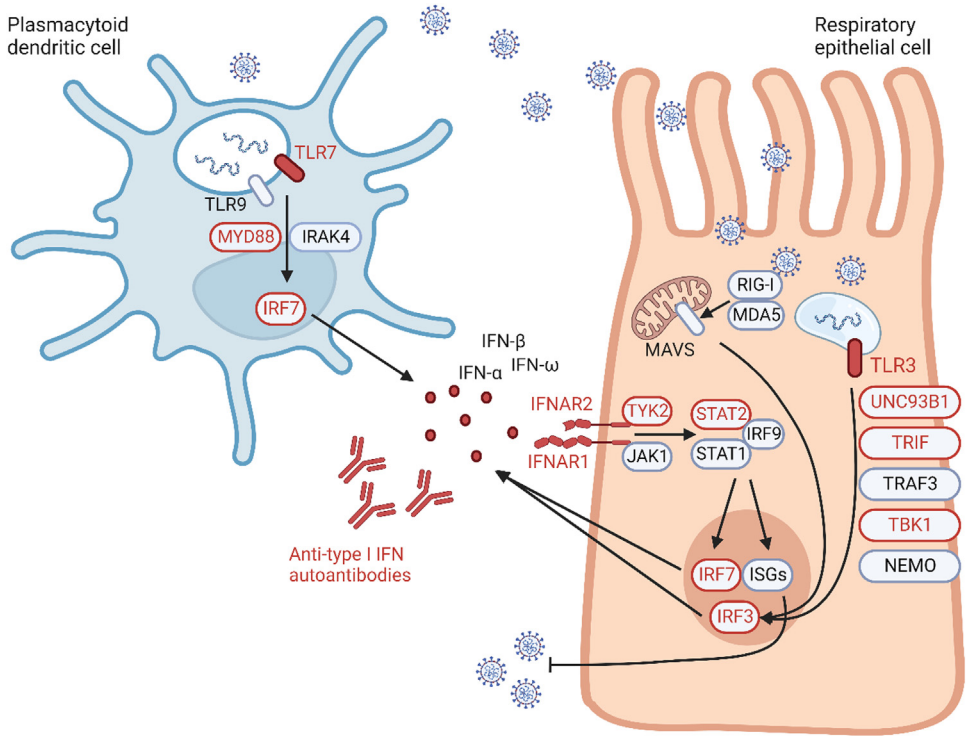

FIG 1. Inborn errors of type I interferon (IFN) immunity and their phenocopies causing susceptibility to severe COVID-19. The activation of the type I IFN responses in respiratory epithelial cells and plasmacytoid dendritic cells following infection with SARS-CoV-2 is illustrated. Viral particles processed through endosomes activate TLR3, TLR7, and TLR9. TLR3 signals through UNC93B1, TRIF, TRAF3, TBK1, and NEMO to induce IRF3. IRF3 is also activated by RIG-I and MDA5, which signal through mitochondrial antiviral signaling (MAVS) following intracellular sensing of viral nucleic acids. TLR7 and TLR9 signal instead via MYD88 and IRAK4 to induce IRF7. Both IRF7 and IRF3 are transcription factors driving the production of type I IFN that in turn bind to their receptor and signal through the STAT1-STAT2-IRF9 complex to induce IRF7 and the transcription of interferon-stimulated genes, which have broad antiviral activities. Monogenic inborn errors of genes involved in these responses were found in patients with critical or fatal COVID-19 and are indicated in red. A phenocopy of these inborn errors is represented by neutralizing autoantibodies against type I IFN, which is also found in a significant proportion of patients with severe COVID-19. (Created with BioRender.)

central nervous system vasculitis, and cytomegalovirus infection), life-threatening yellow fever vaccine associated disease, and critical influenza pneumonia in almost 5% of patients.[71,76-80] Interestingly, in a recent study of 609 patients with SLE, anti–type I interferon autoantibodies were found in 11.7% of patients regardless of age or sex.[71] Only 20 of the 71 samples had neutralizing activity though, and this was significantly associated with episodes of cutaneous herpes zoster and severe viral infection, including increased risk of severe COVID-19. Strikingly, patients with autoantibodies neutralizing several different type I interferons had the highest risk, and these patients were almost uniquely women.[71] This is in line with the data presented by Manry et al, which show that the effect of neutralizing autoantibodies against type I interferons on relative risk of death and infection fatality rate are more important than, for instance, maleness.[30]

MIS-C

Children and young adults are mostly spared from critical COVID-19. However, a few months after the onset of the pandemic, MIS-C emerged as a severe complication usually

affecting children a few weeks after a mild or asymptomatic infection with SARS-CoV-2 in regions in which the incidence of SARS-CoV-2 infection was high.[81-84] MIS-C shows a higher prevalence in males and individuals of African or Hispanic ancestry.[85] Despite overlapping features with Kawasaki disease, MIS-C is often diagnosed in older children (in children aged 7.5-12 years with MIS-C versus in children younger than 5 years with Kawasaki disease), and it has a more severe course with multiorgan dysfunction in more than 70% of patients and shock and myocarditis in 50% and 90% of patients, respectively.[81-84] The hyperinflammatory state is characterized by elevated levels of cytokines and cytopenia, which often fulfil the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).[81-84] As in the case of critical COVID-19 pneumonia, it was hypothesized that specific immune defects could predispose to MIS-C. Early studies reported patients with immune dysregulation syndromes and chronic granulomatous disease (CGD) experiencing extreme inflammation during SARS-CoV-2 infection classified as HLH or MIS-C.[14,86] Subsequently, a prospective targeted sequencing approach unveiled inborn errors of suppressor of cytokine signaling 1 (*SOCS1*; n = 2), X-linked inhibitor of apoptosis (*XIAP*; n = 1) and cytochrome B-245 β-chain (*CYBB*; n = 1) in a cohort of children with MIS-C.[34,35] SOCS1 is a negative regulator of type I and II interferon responses that binds Janus kinase 1 and 2, impeding activation of STAT1 and STAT2 downstream of the interferon receptors. SOCS1 haploinsufficiency has been described in subjects with interferon-driven early-onset familial autoimmunity and lymphoproliferation.[87] Hemizygous loss-of-function mutations in *XIAP* cause immune dysregulation characterized by HLH, inflammatory bowel disease, and inflammation.[88] Finally, CGD is a neutrophil disorder caused by impairment in 1 of the subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which includes the product of *CYBB*. Patients with CGD are prone to invasive pyogenic and fungal infections and granulomatous inflammation. NADPH oxidase defects also predispose to infection-triggered HLH as well as to other noninfectious autoimmune and autoinflammatory manifestations, probably owing to a substantial influx of neutrophils that, although impaired in the oxidative function, can still trigger a strong inflammatory response.[89,90] Chou et al showed an increased inflammatory signature in these children, driven primarily by type I and II interferon and nuclear factor-κB–IL-6 responses.[34] These preliminary findings point to a predisposition to MIS-C in children with inborn errors of immune dysregulation, especially affecting regulators of interferon responses. The significance of these case studies will need to be validated in larger cohorts of patients.

A whole genome/whole exome sequencing approach was used by the COVID Human Genetic Effort to screen a large cohort of 558 children (aged 0-19 years) with MIS-C. By filtering for rare homozygous or hemizygous variants (allele frequency <0.01) in genes involved in antiviral responses, they identified the OAS-RNase L pathway as a relevant signaling circuit in MIS-C.[36] OAS1, OAS2, and OAS3 are interferon-inducible cytosolic dsRNA sensors that activate the endoribonuclease RNase L, which degrades human and viral single-stranded RNA. In this study, 5 patients with autosomal recessive *OAS1*, *OAS2*, or *RNASEL* deficiency caused by biallelic loss-of-function or hypomorphic variants were identified. Variants in these genes were absent from a control group of 1288 patients with mild or asymptomatic infection and a group of 159 children with COVID-19 pneumonia. Interestingly, these variants are estimated to be present in homozygous form in 1 in 10,000 individuals in the general population, which is consistent with the prevalence of MIS-C. As such, AR OAS1, OAS2, or RNASEL deficiency could explain about 1% of MIS-C cases globally. The authors of this same study[36] show that patients' fibroblasts and gene-edited epithelial cell lines lacking *OAS1*, *OAS2,* or *RNASEL* are not more susceptible to SARS-CoV-2 infection, nor are *OAS1*-, *OAS2*-, or *RNASEL*-deleted monocytes more permissive to viral replication. On the other hand, both gene-targeted monocytes and primary monocytes from patients display an exaggerated inflammatory response to dsRNA or SARS-CoV-2 infection, with hyperproduction of several proinflammatory cytokines, such as IL-6, CXCL9, CXCL10, and TNF (the levels of which are also elevated in the serum of patients with MIS-C), and with an upregulated proinflammatory gene expression profile at the transcriptomic level. Thus, in the absence of functional OAS-RNase L signaling, hyperinflammation is driven by activation of the RIG-I and melanoma differentiation-associated protein 5 (MDA5)–mitochondrial antiviral signaling (MAVS) pathway in response to cytosolic dsRNA sensing in monocytes. The reason why there is typically a delay of several weeks between the original infection and the onset of hyperinflammation in children with MIS-C currently remains unexplained.[36]

Finally, several other groups have screened cohorts of children with MIS-C by means of exome sequencing or targeted panels and have found enrichment in rare variants in genes related to autoimmunity, autoinflammation, and immune dysregulation, including genes underlying HLH (*LYST, STXBP2, UNC13D, PRF1, AP3B1,* and *DOCK8*) and genes involved in the interferon responses (*IFNB1, IFNA21, IFNA4, IFNA6, IFIH1, TLR3, TRAF3, IRF3, IFNAR1,* and *IFNAR2*); however, most of these studies do not functionally validate the pathogenicity of the variants and the correlation therefore remains only hypothetical.[18,91-93]

DISCUSSION

The emergence of SARS-CoV-2 in December 2019 and into early 2020 has had a devastating impact worldwide. However, it has also provided the rare opportunity of studying a novel pathogen in a completely naive population. As expected from our knowledge of the human genetics of critical influenza, type I interferons are central to the human immunologic defense in COVID-19.

A defective type I interferon response in the first phases of the viral infection correlates with more severe disease and sustained viremia driving hyperinflammation and multiorgan involvement at a later stage.[94] A 2-phase pathophysiologic model has been proposed; according to this model, uncontrolled viral infection due to a defective type I interferon response in several inborn errors of interferon immunity is followed by hyperactivation and recruitment of leukocytes, which ultimately lead to excessive inflammation.[36,38,86,95,96] Studies investigating the genetic and immunologic determinants of critical COVID-19 have confirmed the crucial role of type I interferon immunity by revealing inborn errors of type I interferon immunity and their autoimmune phenocopies underlying critical or fatal COVID-19 (Tables I and II), as well as common polymorphisms conferring a higher risk of severe infection. Some of these defects had previously been shown to underlie critical influenza pneumonia (*TLR3* and *IRF7*) or other severe viral infections (*IFNAR1*, *IFNAR2*, *STAT2*, *IRF3*, *TBK1*,

UNC93B1, and *TRIF*), whereas defects of TLR7 were discovered as a novel cause of x-linked recessive severe COVID-19 pneumonia.[15,16,18-21,25] These examples highlight the redundancy of most of these mediators of type I interferon immunity in as much as pathogenic loss-of-function variants confer susceptibility to a very narrow spectrum of viruses. Thus, TLR7 seems redundant in human defense against influenza but necessary for defense against COVID-19. Similarly, neutralizing autoantibodies against type I interferon are responsible for up to 20% of critical and fatal COVID-19 cases and were found in only 5% of patients with critical influenza pneumonia.[28,29,79] T-cell defects typically predispose to severe infection with a broad range of viruses and opportunistic pathogens, so an increased morbidity and mortality would be expected in patients with combined immune defects. This is confirmed by the finding of an extremely elevated fatality rate in children with severe combined immunodeficiency before transplantation, whereas survival was 100% in children who were infected with SARS-CoV-2 after curative procedures.[14,97-102] Very few severe or lethal cases have been reported in patients with combined immunodeficiencies other than severe combined immunodeficiency, possibly indicating a subtle role of T-cell immunity in clearing SARS-CoV-2 compared with the robust contribution of type I interferon responses.[39] On the other hand, the pathophysiologic mechanism underlying MIS-C seems to be an exacerbated inflammatory process in which the type I and II interferons, IL-6, and RIG-I-MDA5-MAVS pathways play a central role and the monocytes are the key drivers of inflammation, as confirmed by reports of several inborn errors of immune dysregulation (defects of *SOCS1*, *XIAP,* and *CYBB*) and RNA degradation (defects of *OAS1*, *OAS2,* and *RNASEL*) in children with MIS-C.[34-36]

On the basis of these findings, attempts to devise a therapeutic strategy based on modulating the interferon response have been proposed.[37] A very fine balance between initial activation of antiviral and inflammatory responses to control the viral spread and subsequent downtuning of the inflammation to avoid organ damage seems to be required. The in-depth study of patients with critical COVID-19 in terms of genetic and immunologic determinants has undoubtedly expanded the awareness of the genetic (and immunologic) theory of infectious diseases beyond the realm of clinical immunology, reaching intensive care physicians and beyond. Novel inborn errors have been and will continue to be described in the context of critical COVID-19, furthering our knowledge and understanding of human immunology. Moreover, ongoing research will aid in understanding other manifestations of COVID-19, including long-COVID and neuro-COVID, which will in turn shed light on the postinfectious manifestations identified in other infections and their systemic and neurologic sequelae.

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