

Infection-induced inflammation from specific inborn errors of immunity to COVID-19

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Inborn errors of immunity (IEIs) are a group of genetically defined disorders leading to defective immunity. Some IEIs have been linked to mutations of immune receptors or signaling molecules, resulting in defective signaling of respective cascades essential for combating specific pathogens. However, it remains incompletely understood why in selected IEIs, such as X-linked lymphoproliferative syndrome type 2 (XLP-2), hypo-immune response to specific pathogens results in persistent inflammation. Moreover, mechanisms underlying the generation of anticytokine autoantibodies are mostly unknown. Recently, IEIs have been associated with coronavirus disease 2019 (COVID-19), with a small proportion of patients that contract severe COVID-19 displaying loss-of-function mutations in genes associated with type I interferons (IFNs). Moreover, approximately 10% of patients with severe COVID-19 possess anti-type I IFN-neutralizing autoantibodies. Apart from IEIs that impair immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), SARS-CoV-2 encodes several proteins that suppress early type I IFN production. One primary consequence of the lack of type I IFNs during early SARS-CoV-2 infection is the increased inflammation associated with COVID-19. In XLP-2, resolution of inflammation rescued experimental subjects from infection-induced mortality. Recent studies also indicate that targeting inflammation could alleviate COVID-19. In this review, we discuss infection-induced inflammation in IEIs, using XLP-2 and COVID-19 as examples. We suggest that resolving inflammation may represent an effective therapeutic approach to these diseases.

Abbreviations

APS-I, autoimmune polyendocrine syndrome I; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DAMP, damage-associated molecular pattern; EBV, Epstein–Barr virus; HLH, hemophagocytic lymphohistiocytosis; IEIs, inborn errors of immunity; IFN, interferon; IFNAR1/2, IFN- α receptor 1/2; IL, interleukin; IRF, IFN regulatory factor; ISG, interferon-stimulated gene; M protein, membrane protein; MERS-CoV, Middle East respiratory syndrome coronavirus; MMR, measles, mumps, and rubella; MSMD, Mendelian susceptibility to mycobacterial disease; N protein, nucleocapsid protein; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; NOD2, nucleotide-binding oligomerization domain-containing protein 2; NSP, nonstructural protein; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor, S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOCS1, suppressor of cytokine signaling 1; STAT1, signal transducer and activator of transcription 1; TLR, Toll-like receptor; Treg cell, regulatory T cell; XIAP, X-linked inhibitor of apoptosis protein; XLP-2, X-linked lymphoproliferative syndrome type 2.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that is causing the human coronavirus disease 2019 (COVID-19) pandemic. SARS-CoV-2 was first identified in December 2019, and as of April 2, 2021, the COVID-19 pandemic has led to over 130 million infections and more than 2.8 million deaths worldwide. Like other coronaviruses (CoVs), including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is a positive-sense single-stranded RNA virus [1]. The 29.9-kilobase SARS-CoV-2 genome encodes the viral spike (S), envelope (E), membrane (M), and nucleocapsid (N) structural proteins, as well as 16 nonstructural proteins (nsp1–nsp16) [1,2]. The S, E, and membrane protein (M proteins) form the viral envelope that encapsulates the viral nucleocapsid consisting of nucleocapsid protein (N protein) and genomic RNA. S protein binds to angiotensin-converting enzyme 2 (ACE2), its receptor on host cells, to trigger fusion of the viral particle with the host cell membrane, enabling delivery of the viral RNA genome into the cytoplasm of the host cell. SARS-CoV-2 infection can be asymptomatic or symptomatic, with ~20% of symptomatic patients developing severe pneumonia and dyspnea, which can be accompanied by numerous complications and even death. Despite intensive global efforts to characterize SARS-CoV-2 infection, the pathogenic mechanism underlying COVID-19 remains incompletely understood [3–5].

Inborn errors of immunity (IEIs), also known as primary immunodeficiencies, are a group of genetically defined disorders leading to defective innate or adaptive immunity. Which immune responses are impaired depends on the associated genetic mutation [6]. For example, mutation of genes involved in the recombination of immunoglobulins and T-cell receptors, such as *RAG*, *DNA-PK*, or *DNA ligase IV*, induces severe combined immune deficiency (SCID) because adaptive immunity is abrogated. Other IEIs include those leading to antibody deficiency, immune dysregulation, congenital defects in phagocytes, autoinflammatory disorders, complement deficiencies, or autoantibody generation [6]. Some IEIs confer susceptibility to infection by specific pathogens, such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), *Candida*, or mycobacteria [7]. The pathogenic mechanisms of some IEIs can be directly inferred from gene impairment; for example, the inability to tackle any infection in the case of SCID is due to the absence of B cells and T cells, while deficiency in interleukin (IL)-6R signaling molecules fails to induce T helper 17

(Th17) and to control pyrogenic bacterial infection and fungal infection [6]. For a few IEIs, such as X-linked lymphoproliferative syndrome type 2 (XLP-2), despite the identity of a mutated immune receptor or signaling molecule being known, it remains incompletely understood how an initial hyporesponse to the specific pathogen exacerbates inflammation.

With regard to COVID-19, ongoing efforts to characterize in detail immune responses to SARS-CoV-2 have revealed early ineffective innate immune responses and an eventual inflammatory storm in patients with severe COVID-19. Moreover, type I interferon (IFN) autoantibodies and mutation of several type I IFN-associated genes have been identified in a subpopulation of such patients [8,9], revealing a pivotal role of type I IFN to control SARS-CoV-2 and of host immune defect in the pathogenesis of severe COVID-19 infection. Furthermore, SARS-CoV-2 suppresses the expression and signaling of type I IFNs, leading to excess inflammation. In this review, we discuss recent progress in studying anti-IFN antibodies and IEIs involving XLP-2 and IFN, as well as their relevance to infection-induced inflammation in COVID-19 [10].

Inborn errors of immunity

Up to 430 IEIs have been documented, and they have been classified into 10 categories by the International Union of Immunological Societies Expert Committee [6]. IEIs are often associated with inflammation. Certain IEIs involve gain-of-function mutations in genes encoding, for example, inflammasome components such as NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3), pyrin, NLRP1, or NLRC4, yielding constitutively active inflammasomes that induce auto-inflammation [11]. Mutations that generate deficiency of negative signaling molecules, such as *Foxp3* or *IL-10R*, also lead to uncontrollable inflammation. For other IEIs, inflammation is attributable to infection [12]. Notably, the sensitivity to pathogens cannot be directly inferred from the function of the mutated gene, with varying degrees of redundancy in pathogen sensitivity [13]. For instance, despite that *IRAK4* and *MyD88* are the mediators of several Toll-like receptor (TLR) signaling, both deficiencies are indispensable for controlling pyrogenic bacteria but not for most other pathogens [14,15]. Likewise, TLR3 deficiency selectively impairs immunity to some viral infections, such as herpes simplex virus encephalitis [16]. Autosomal recessive mutation of *UNC93B*, encoding a protein essential for the production of type I/III IFNs, impairs TLR3 response and induces development of herpes

simplex virus 1 (HSV-1) encephalitis (HSE), but patients respond normally to other TLRs and viruses [17]. In addition to this unpredictable sensitivity to selective pathogens, an unresolved question is how disruption of a pro-inflammatory signal leads to the inflammatory disorder associated with infection-linked IEs. For example, XLP-2 represents a specific type of IEI in which an initial hyporesponse to EBV infection results in persistent inflammation characterized by hemophagocytic lymphohistiocytosis (HLH). XLP-2 is selected for discussion in this review because of the similarity with severe COVID-19 in which defective early immunity leads to uncontrollable inflammation. Additionally, the generation of anti-IFN- γ autoantibodies, with unknown mechanism, shows a phenocopy of inborn error of IFN- γ pathway deficiencies, which confers susceptibility to specific infection [18]. An analog was found in a fraction of severe COVID-19 patients carry anti-type I IFN antibodies [8]. In this review, focusing on the relevance to COVID-19, we limit our discussion on IEIs of XLP-2 and IFNs, and autoantibodies to IFNs.

Infection-induced inflammation in XLP-2

Signaling defects associated with XLP-2

XLP-2 is an IEI caused by a deficiency in X-linked inhibitor of apoptosis protein (XIAP) [19–21]. XLP-2 is often associated with infection from EBV, resulting in excess cytokine production and HLH due to hyperactivation of lymphocytes and macrophages [22]. Recent studies have revealed that *XIAP* mutation also contributes to pediatric-onset Crohn's disease in some patients [23–25]. Even though XIAP is an anti-apoptotic protein that specifically inactivates caspase-3, caspase-7, and caspase-9 [26], it also participates in several critical immune signaling cascades independently of its anti-apoptotic function.

Figure 1 summarizes the known signaling processes mediated by XIAP. The best-characterized signaling defect in XIAP-deficient cells relates to the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) pathway (Fig. 1A). XIAP interacts with receptor-interacting protein kinase 2 (RIPK2), the scaffold protein that mediates NOD2 activation, by introducing K63 poly-ubiquitination on RIPK2 for signalosome formation, leading to MAPK and NF- κ B activation and the expression of pro-inflammatory cytokines [27–30]. NOD2 is a cytoplasmic pattern recognition receptor (PRR) that senses bacterial

peptidoglycan fragments containing muramyl dipeptide (MDP). Consequently, XIAP deficiency impairs NOD2 signaling, accounting for the failure of *Xiap*^{-/-} mice to handle *Listeria monocytogenes* infection [31].

Canonical NF- κ B activation and the TNF/IL-6 production induced by various TLRs are intact in *Xiap*^{-/-} cells [28,31–33], and XIAP deficiency impairs the dectin-1-induced NF- κ B activation mediated by BCL10 [33] (Fig. 1). XIAP promotes BCL10 K63 ubiquitination and stabilizes BCL10. In the absence of XIAP, BCL10 levels are downregulated, resulting in diminished dectin-1-initiated NF- κ B activation and TNF/IL-6 production [33]. Defective dectin-1 signaling results in *Xiap*^{-/-} mice being incapable of controlling *Candida albicans* infection [33].

XIAP deficiency also leads to defects in regulatory T (Treg) cells [34]. Tregs are critical components for maintaining peripheral immune tolerance [35]. XIAP-deficient Tregs appear normal, but inflammatory cues can reprogram them into IFN- γ -secreting cells [34]. *Foxp3* expression is reduced in *Xiap*^{-/-} regulatory T cell (Treg cells), and they lost suppressive functions. These *Xiap*^{-/-} Treg cell defects have been linked to downregulated expression of suppressor of cytokine signaling 1 (SOCS1; Fig. 1), a negative regulator of cytokine signaling that stabilizes *Foxp3* expression by suppressing signal transducer and activator of transcription 1 and 3 (STAT1- and STAT3)-directed IFN- γ and IL-17 production [36]. XIAP binds SOCS1 and promotes its stabilization [34].

XIAP knockout does not affect the sensitivity of thymocytes, conventional T cells, and embryonic fibroblasts to cell death [37]. However, XIAP deficiency confers susceptibility to apoptosis on invariant natural killer (iNKT) cells and mucosal-associated invariant T (MAIT) cells, with enhanced expression of caspase-3, caspase-7, and BH3-interacting domain death agonist (BID) in iNKT cells [38]. In contrast, XIAP-deficient myeloid cells are prone to inflammasome activation. Inflammasome activation requires two signals: one from innate receptors to activate the expression of NLRP3 and pro-IL-1 β , and a second danger signal to promote inflammasome assembly [39,40]. In the absence of XIAP, TLR signal treatment alone drives RIPK3-caspase-8-mediated NLRP3 inflammasome activation, circumventing the requirement for a second signal [41,42]. The susceptibility of *Xiap*^{-/-} myeloid cells to inflammasome activation implies that the inflammatory cues generated by infection in XIAP-null individuals arise from inflammasomes. Apart from Tregs, it is interesting to note that XIAP deficiency primarily affects signaling in myeloid cells.

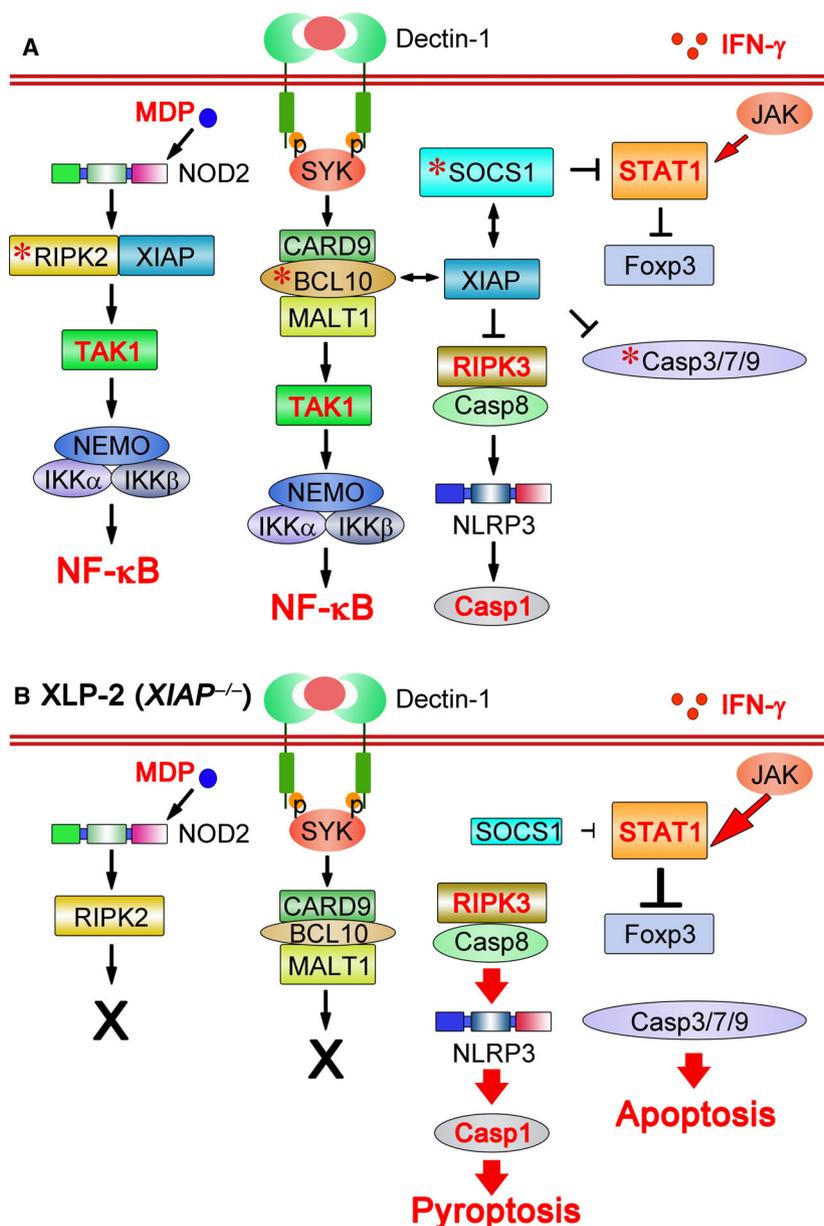


Fig. 1. Signaling defects in XIAP-deficient individuals. (A) XIAP regulates NOD2, dectin-1, and Treg cells by binding to RIPK2, BCL10, and SOCS1. Binding of XIAP to RIPK2 polyubiquitinates RIPK2 and activates NOD2 signaling [27–30]. XIAP also binds and stabilizes BCL10 to enable dectin-1 signaling [33]. Interaction of XIAP with SOCS1 stabilizes this latter, helping to maintain regulatory T-cell populations by suppressing IFN- γ -STAT1 signaling [34]. XIAP also inhibits RIPK3 and caspase-8-mediated NLRP3 inflammasome activation [41,42]. Moreover, it binds and inactivates caspase-3, caspase-7, and caspase-9. *, XIAP-interacting protein. That most TLR activation is XIAP-independent is not shown in the figure. (B) Infection by EBV, *Listeria monocytogenes* or *Candida albicans* induces signaling defects in XLP-2 (XIAP-deficient) cells. As a consequence of XIAP loss, the NOD2 signaling cascade is blocked and dectin-1-initiated signal transduction is diminished. In addition, reduced SOCS1 levels fail to antagonize STAT1-directed FoXP3 destabilization, leading to attenuated Treg function. The absence of XIAP also facilitates caspase-8-dependent NLRP3 inflammasome activation, bypassing the dual signal requirement, resulting in caspase-1 activation and pyroptosis. XIAP deficiency increases the activity of caspase-3, caspase-7, and caspase-9 for apoptosis induction. Most TLR signaling activity remains intact, leading to TNF expression, which primes necroptosis.

Infection-induced inflammation in XLP-2

Epstein–Barr virus is the primary pathogen triggering XLP-2 syndromes in humans. The predominance of EBV infection associated with XLP-2 is likely linked to the prevalence (90%) of EBV in adults, meaning that XLP-2 infants are exposed early to EBV. The exact mechanism of how EBV induces XLP-2 syndrome remains unclear [43]. In healthy individuals, control of EBV infection is highly dependent on CD8⁺ T cells [44,45]. Notably, EBV-specific CD8⁺ T cells from XLP-2 patients exhibit effector-memory phenotypes and elicit strong IFN- γ production against EBV extracts [46],

indicating an intact efficacy of EBV-specific CD8⁺ T cells. In contrast, impaired NOD2 signaling in XLP-2 patients may explain their susceptibility to Crohn’s disease [47]. NOD2 binds MDP derived from bacterial peptidoglycans, and mutation of *NOD2* is linked to a higher risk of Crohn’s disease (for review, see [48]). It is generally believed that by sensing MDP from microbiota, NOD2 confers protective immunity against harmful intestinal bacterial. Defective NOD2 signaling due to XIAP deficiency thereby increases the risk of Crohn’s disease.

Xiap^{-/-} mice can be used to understand how infection triggers inflammation in XLP-2 patients. XIAP

knockout mice are normal when housed in specific pathogen-free (SPF) environments [37,49,50]. However, they become vulnerable upon infection by selected pathogens, including *L. monocytogenes*, *Chlamydomyphila pneumoniae*, *C. albicans*, or murine γ -herpesvirus 68, displaying XLP-2-like syndromes and high mortality [31,33,41,51]. By using a low-dose *C. albicans* treatment survived by all wild-type (WT) mice, the susceptibility of XIAP-deficient mice to pathogen was shown to be a consequence of infection-induced inflammation [33]. Consistent with defective dectin-1 signaling, serum levels of TNF, IL-6, and MCP-1 were significantly lower in *Xiap*^{-/-} mice than WT mice 4 h after *C. albicans* infection treatment. In contrast, high inflammatory cytokine levels were detected in *Xiap*^{-/-} mouse after 1 week, correlating with the high fungal loads, indicating that inflammation is a consequence of pathogen persistence [33]. Almost all *Xiap*^{-/-} mice succumbed to *C. albicans* within 15 days of infection.

The mortality associated with infection in XIAP-deficient mice may be rescued by targeting inflammation. During inflammation, prostaglandins (eicosanoids) activate the generation of pro-resolving lipid mediators—including resolvins, protectins, and lipoxins. These eicosanoids act in various ways to resolve inflammation [52,53]. Administration of resolvin D1 effectively suppresses *C. albicans* infection-induced inflammatory cytokine generation and prevents infection-triggered mortality in *Xiap*^{-/-} mice [33]. Transfer of XIAP-sufficient Tregs after *C. albicans* infection also rescued *Xiap*^{-/-} mice from infection-induced death [34], accompanied by nearly complete abrogation of inflammatory cytokine. While infection in many IEIs needs antimicrobial treatment, these results illustrate an extreme case in IEI that infection-induced inflammation is a dominant cause of pathogenesis and lethality and that resolution of inflammation is sufficient to control infection in the absence of antimicrobial reagents.

Figure 2 is a summary on how XIAP deficiency confers infection-induced uncontrollable inflammation in XLP-2. Upon infection by the pathogens that XIAP-null myeloid cells cannot handle (such as EBV, *L. monocytogenes*, or *C. albicans*), the pathogens continuously multiply, leading to excess tissue damage and cell death. That cell death plays a critical role in the transition from hypo-immune responses to inflammation. XIAP-deficient cells are more vulnerable than their normal counterparts to induction of pyroptosis, apoptosis, and necroptosis. The low threshold of inflammasome activation in XIAP-null cells elevates caspase-1 production and enhances pyroptotic death [41,42] (Fig. 1B). Loss of XIAP removes suppression

of caspase-3, caspase-7, and caspase-9 and enhances apoptotic death (Fig. 1B), as observed in iNKT and MAIT cells [38]. TLRs and TNFR signaling mostly remain intact in XIAP-deficient myeloid cells [28,31–33], allowing TNF generation and TNF-directed necroptosis and apoptosis [54,55]. Excessive pathogen-associated molecular patterns (PAMPs) as a result of prolonged pathogen presence, together with the generation and release of damage-associated molecular patterns (DAMPs) in the death process, act as persistent stimuli to activate innate immune receptors. The intact TLR and other innate immune receptor signaling cascades in XIAP-deficient myeloid cells respond to emerging DAMPs, facilitating low-responding XIAP-null myeloid cells to convert to high inflammatory cytokine-producing cells. Compounding the extent of inflammation, CD8⁺ T cells are fully reactive to EBV in XLP-2 patients, fueled by inflammatory antigen-presenting cells (e.g., dendritic cells), which generate the large amounts of IFN- γ that contribute to HLH. Anti-IFN- γ -neutralizing antibodies have been approved for use in pediatric primary HLH patients, even though not directly on XLP-2 patients, before standard hematopoietic stem cell transplantation [56,57], indicating that blockade of IFN- γ -mediated inflammation alleviates HLH symptoms. It is interesting to note that anti-IFN- γ plus anti-TNF treatment effectively prevents experimental HLH induced by poly I:C plus LPS [58]. Therefore, pathogen-induced cell death, DAMP/PAMP-mediated activation of innate signaling, and inflammatory cell death together control the switch from an initial low-level response to the persistent inflammation seen in IEIs like XLP-2.

IEIs associated with lack of interferons

Human immunodeficiency of IFN- γ

Interferons, first identified in 1957, are a group of cytokines that play critical roles in endowing immunity to infectious diseases [59]. Based on their cognate receptors, IFNs can be classified into three different groups, that is, types I, II, and III. Below, we discuss the role of these IFNs in human immunity, with a particular focus on type I and type II IFNs. Figure 3 is a summary of the role of IFN- γ —the sole type II IFN, in host immunity to microbes. IFN- γ is exclusively produced by T cells and natural killer (NK) cells—forms a homodimer and binds to heterodimeric IFN- γ receptor comprising IFN- γ R1 and IFN- γ R2 (IFNGR1, IFNGR2) subunits. The resultingly activated IFN- γ receptor induces STAT1 phosphorylation

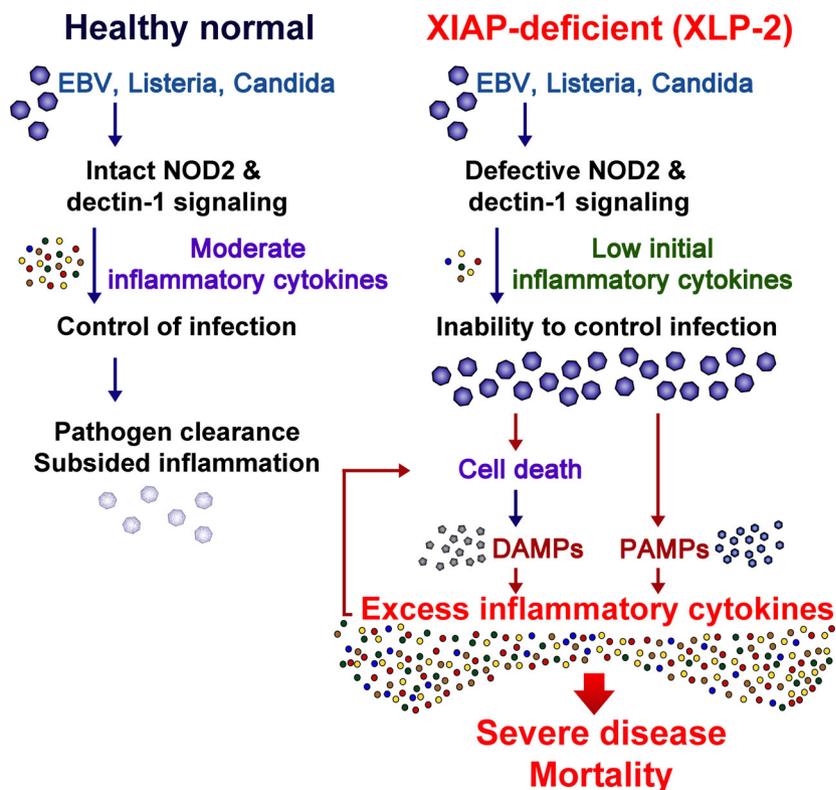


Fig. 2. How does infection trigger persistent inflammation in XLP-2? During infection by EBV, *Listeria monocytogenes*, or *Candida albicans* in normal healthy individuals (left), intact innate immunity generates moderate amounts of inflammatory cytokines such as TNF, IL-6, and IFN- γ that help control pathogen replication. Consequently, the pathogens are cleared and inflammatory cytokines subside. In contrast, XIAP-deficient individuals cannot handle the same infections due to defective NOD2 and dectin-1 signaling pathways (right). Accordingly, inflammatory cytokine levels are low upon immediate infection. The inability to control the pathogen results in increased pathogen load and PAMPs. Moreover, XIAP-deficient cells are more susceptible to apoptosis, pyroptosis, and necroptosis, leading to the release of DAMPs. This buildup of PAMPs and DAMPs results in persistent release of inflammatory cytokines that further induce inflammatory cell death. The excess in inflammatory cytokines leads to severe disease and mortality.

via receptor-associated JAK1 and JAK2 proteins. Phosphorylated STAT1 forms a homodimer, enabling it to bind to conserved IFN- γ activation sites (GAS) in DNA elements to drive the transcription of interferon-stimulated genes (ISGs) [60,61]. IFN- γ receptor, like IFN- α receptor (IFNAR), is expressed in most cell types, but IFN- γ is well-known as a key factor in macrophage activation, and macrophages are the major target for IFN- γ -mediated activity [62].

In humans, how IFNs function in immunity against infectious diseases has been further illustrated by studying IFN-related inborn genetic disorders. Mendelian susceptibility to mycobacterial disease (MSMD) features a selective and inherited predisposition to nonvirulent mycobacteria and other intramacrophagic pathogens. To date, 17 gene disorders have been found in patients with MSMD [63,64]. Even though it can arise via mutation of various genes, MSMD presents

physiological homogeneity in that all contributory genetic causes to MSMD affect IFN- γ -dependent pathways. The affected genes encode proteins involved in inducing either IFN- γ production [IL-12B, IFNG, IL12RB1, IL12RB2, ILR23R, ISG15, TYK2, IKBKG, IFN regulatory factor 8 (IRF8), RORC, SPPL2A, and T-BET] or control IFN- γ function (IFNGR1, IFNGR2, JAK1, STAT1, and CYBB). However, viral infection is less commonly observed in IFN- γ -deficient MSMD patients [65].

Anti-IFN- γ autoantibodies

Anticytokine autoantibodies represent an emerging etiology causing immune dysregulation in human diseases [18]. By binding to cognate cytokines, autoantibodies interrupt signaling transduction and impair the biological functions of cognate cytokines,

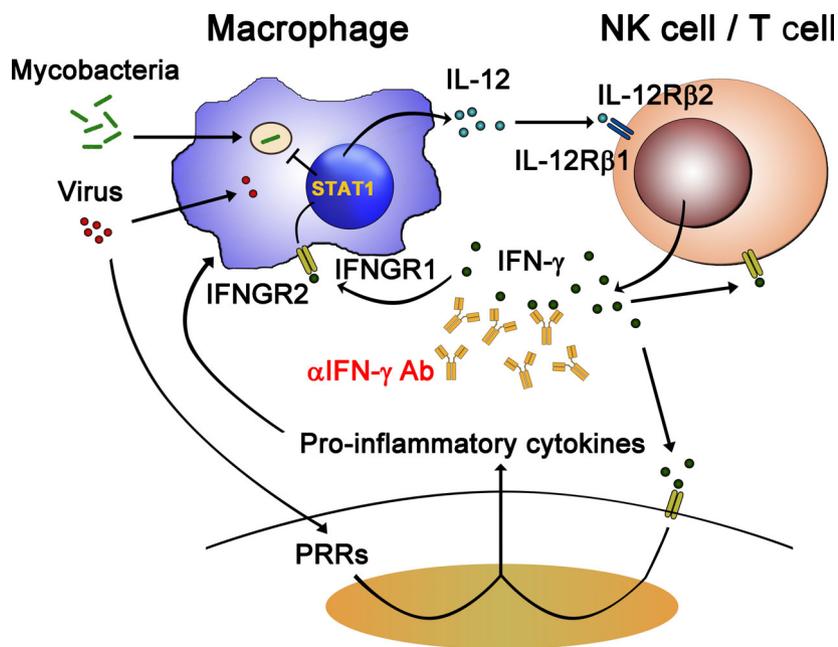


Fig. 3. Role of IFN- γ in host immunity to microbes. Intramacrophagic pathogens (such as mycobacteria) infect macrophages and strongly induce production of IL-12, which binds IL-12 receptors (IL-12R β 1 and IL-12R β 2 heterodimer) and activates T/NK cells to produce IFN- γ . IFN- γ then binds IFN- γ receptors (IFNGR1 and IFNGR2 heterodimer), enabling STAT1 activation and expression of ISGs to eliminate the engulfed microbes. IFN- γ also stimulates other cell types to induce ISG expression in a similar way. Anti-IFN- γ autoantibodies have been identified in adult patients with disseminated mycobacterial infections [18]. The direct role of IFN- γ in antiviral responses has not been established. During viral infection, cells recognize viral invasion through PRRs and they produce pro-inflammatory cytokines. The pro-inflammatory cytokines further enhance IFN- γ production. The synergistic effects of IFN- γ and pro-inflammatory cytokines may orchestrate the host immune system to tackle the viral invasion. However, hyperactivity of this pro-inflammatory response may also cause cytokine release syndrome and cause host tissue damage. Thus, blocking these over-reacting cytokine responses by means of anticytokine antibodies, such as anti-IFN- γ antibodies, might have a clinical benefit.

leading to physiological dysregulation in patients. Therefore, anticytokine autoantibodies are deemed a late-onset immunodeficiency [6,66]. Anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies were the first anticytokine autoantibodies to be comprehensively characterized as causing human disease [67]. The presence of these autoantibodies halts maturation of alveolar macrophages by blocking the function of GM-CSF and leading to pulmonary alveolar proteinosis, which is a pathological indication of surfactant accumulation in lung tissue [68]. The disease relevance of anticytokine autoantibodies is reinforced by the fact that patients harboring autoantibodies to various cytokines are being increasingly identified, including against IFNs γ and α , as well as IL-12, IL-6, and IL-17 [18,69–76]. Among them, IFNs (including IFN- γ and some type I IFNs) are the most common targets of the autoantibodies reported in patients with various clinical manifestations. Notably, the genetic basis of anticytokine autoantibodies remains mostly unknown, as they are

catalogued under ‘Phenocopies of IEI’ defined by IUIS Expert Committee [6].

Anti-IFN- γ autoantibodies were first reported in a small group of adult patients displaying disseminated mycobacterial infections. Similar to MSMD patients, the autoantibodies block signaling of endogenous IFN- γ via IFN- γ receptors [71,72]; therefore, autoantibodies to IFN- γ phenocopy MSMD in adults [77]. Initially, this trait was considered a very rare illness, but patients with these autoantibodies are being increasingly reported over the last decade and primarily from South-East Asia, South China, and Japan [18,78,79]. Interestingly, anti-IFN- γ autoantibody production is strongly linked to specific HLA class II alleles (DRB1*16:02/DQB1*05:02 in patients from South China and Taiwan, or DRB1*15:02/DQB1*05:01 in those from South-East Asia) [80]. These two alleles are almost exclusively found in those regions, providing further genetic evidence of the restricted geography of this autoantibody-related disease. Recently, anti-IFN- γ autoantibodies were reported as the major etiology of

Talaromyces marneffei infection—a dimorphic fungal pathogen only distributed in South China and South-East Asia—in nonhuman immunodeficiency virus-infected patients from South China [81,82]. Thus, through both inborn genetics and autoantibodies, IFN- γ has been demonstrated to play critical roles in controlling mycobacterial and intramacrophagic pathogens, such as bacteria and fungi (Fig. 3).

Viral infection and IFN- γ

Similar to other human viral infections, SARS-CoV-2 infection results in a broad spectrum of clinical manifestations, from asymptomatic cases to fatalities. Activation of the immune system and production of inflammatory cytokines are essential processes in natural antiviral immune responses. However, hyperactivation of the immune system results in an acute increase in pro-inflammatory cytokines, which can cause cytokine release syndrome (CRS) [83]. High levels of serum inflammatory cytokines are observed in patients with severe COVID-19 [58,84–89]. In severe cases of SARS-CoV-2 infection, patients suffer systemic symptoms of varying severity, including acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS), both of which are associated with aggressive inflammatory responses and elevated levels of pro-inflammatory cytokines. CRS is associated with lung injury, multiple organ failure, and mortality [90,91].

It is generally recognized that type II IFN is responsible for antimycobacterial responses. What role IFN- γ plays in controlling SARS-CoV-2 infection remains largely unknown. Relative to type I IFNs, its role in viral infections is not prominent. However, IFN- γ treatment does induce strong STAT1 activation and protection from viral invasion in *in vitro* cell models. IFN- γ treatment also inhibited SARS-CoV-2 replication *in vitro* [92]. The antiviral potential of IFN- γ is further supported by the fact that varicella zoster virus (VZV) reactivation is observed in approximately one-third of patients harboring anti-IFN- γ autoantibodies, and some sporadic cases of CMV, HSV, or VZV infection have been reported in patients with IFN- γ receptor deficiency [93]. Moreover, IFN- γ plays multiple roles in myeloid cell activation and can influence maturation of adaptive immunity, which may affect the development of adequate innate and adaptive immunity to SARS-CoV-2 infection. Elevated IFN- γ levels have been reported in some cases of COVID-19-associated severe pneumonia and other CRS [94,95]. Indeed, among the elevated cytokines induced by SARS-CoV-2 infection, IFN- γ and TNF are the two major ones

that together cause massive cell death [58]. Notably, an IEI patient with *STAT1* gain-of-function was asymptomatic after SARS-CoV-2 infection [10]. Nevertheless, to our knowledge, no IFN- γ -deficient patient, with either IEI in IFN- γ pathway or anti-IFN- γ autoantibodies, with SARS-CoV-2 infection, has been reported.

Immunodeficiency in type I IFN with viral infection

At least 17 type I IFN functional genes have been reported in humans (including 12 subtypes of IFN- α , IFN- β , IFN- ω , IFN- ϵ , and IFN- κ) [96]. Figure 4 summarizes IFN-I and TLR3 responses to viral infection. Type I IFNs bind to heterodimeric IFNARs and induce dimerization of receptor subunit IFNARs 1 and 2 (IFNAR1, IFNAR2). Activation of these IFNARs further induces phosphorylation of STAT1 and STAT2 via Janus kinase 1 (JAK1) and tyrosine kinases (such as TYK2). Phosphorylated STAT1/STAT2 interacts with IRF9 to form the ISGF complex, which binds to the IFN-sensitive response element (ISRE) on chromosomes to enhance transcription of hundreds of IFN-stimulated genes (ISGs) [61,97,98].

Type I IFNs are well characterized for their potent antiviral effects *in vitro* and *in vivo*. The role of type I IFN-mediated antiviral immunity has recently re-emerged due to the identification of inborn errors in type I IFN- and IFNAR-deficient patients. STAT2 is involved in type I and type III IFN signaling pathways, and STAT2 deficiency has been found in patients suffering from severe viral infections upon receipt of live-attenuated vaccine against measles, mumps, and rubella (MMR) [99]. A patient displaying MMR vaccine-related disease and life-threatening influenza possessed a mutant version of IRF9, a component of the transcriptional activator complex ISGF3 together with STAT1 and STAT2 [100]. Genuine human type I IFN deficiency was illustrated by the identification of the first person with an IFNAR2 deficiency that abolished type I IFN signaling, which was described in a child that suffered fatal encephalitis after being inoculated with MMR vaccine [101]. A severe adverse reaction to MMR vaccine has also been reported in a family displaying IFNAR1 deficiency. Similarly, viscerotropic disease induced by yellow fever vaccination was also reported for a 14-year-old girl with compound heterozygous IFNAR1 deficiency [47]. These human IFN deficiencies demonstrate that type I IFNs are crucial for protective immunity against live-attenuated vaccines, at least for MMR and yellow

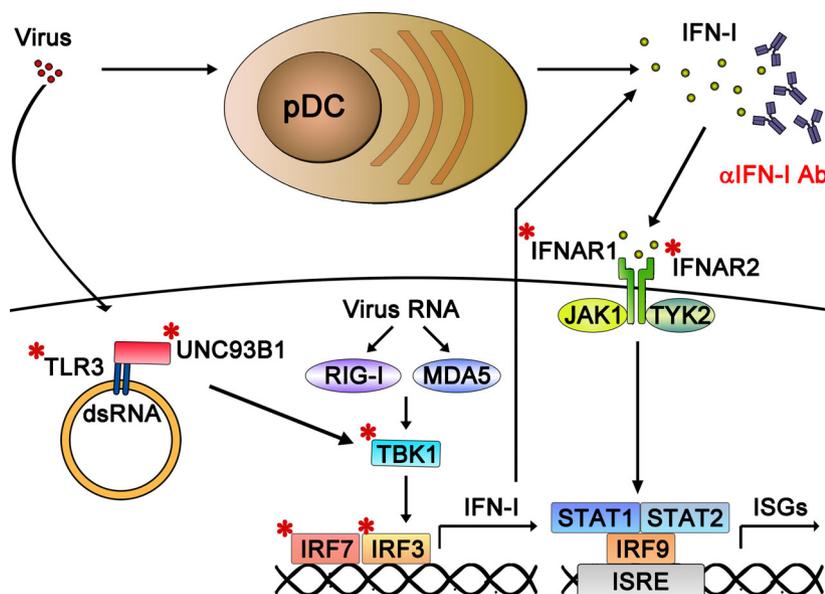


Fig. 4. Virus-induced type I IFN and TLR3 responses and their dysregulation in severe COVID-19 pneumonia. Nonhematopoietic cells sense viral invasion through a panel of PPRs (such as TLR3, RIG-I, MDA-5) and produce type I IFNs by activating IRF3/7. Moreover, plasmacytoid dendritic cells (pDCs) have an extraordinary ability to detect virus and to secrete type I IFNs, particularly IFN- α . These type I IFNs act via autocrine or paracrine modes to induce antiviral immunity in pDCs and surrounding cells through IFNARs (IFNAR1 and IFNAR2 heterodimer). Recently, IEI in the genes encoding TLR3, Unc93B1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2 (marked with *) have been shown to impair induction of type I/III IFN responses to viral infection, and this scenario has been linked to severe COVID-19 disease [9]. Moreover, the presence of neutralizing autoantibodies against IFN- α and IFN- ω , which can block the function of these crucial antiviral cytokines, can also cause severe COVID-19-related pneumonia [8].

fever. Consistent with those results, a partial gain-of-function mutation in IFN-induced helicase C-domain-containing protein 1 (IFIH1; A946T), critical for responses to RNA virus, confers host resistance to lethal encephalomyocarditis virus infection [102].

For anti-IFN-I autoantibodies, anti-IFN- α and anti-IFN- ω autoantibodies are common in patients with autoimmune polyendocrine syndrome I (APS-I), an inherited autoimmune disease caused by mutation in the gene *Autoimmune regulator (AIRE)* responsible for thymic function in developing immunotolerance [103]. Notably, anticytokine autoantibodies are generated precede the onset of APS-I syndromes [104]. Apart from displaying autoimmunity, APS-I patients also suffer various fungal infections, most frequently by chronic mucocutaneous candidiasis. The identification in such patients with neutralizing autoantibodies to IL17A/F and IL22, which are key cytokines in Th17 immunity, explains their susceptibility to fungal infection [76]. Anti-IFN- α and other type I IFN autoantibodies have been found in some patients with other diseases, such as systemic lupus erythematosus [105], Sjögren's syndrome [106], and thymoma [75], and even in healthy individuals [107]. The association between

anti-IFN-I autoantibodies and viral disease has been illustrated by the link of anti-IFN- α autoantibodies to severe VZV infection [108]. More recently, anti-IFN- α autoantibodies are also identified in patients with life-threatening yellow fever vaccine-associated diseases [109].

Type I IFN immunity in COVID-19

Genetic defects of type I IFN immunity in severe COVID-19

Given that severe COVID-19 disease is less frequent in individuals younger than 50 years old, it is possible that the severe disease in these patients is due to an undiagnosed immunodeficiency, particularly in the type I IFN pathway [110]. This notion has been supported by Zhang *et al.* [9], who searched for loss-of-function (LOF) variants at the 13 gene loci known to be involved in type I IFN immunity. They identified LOF variants in 23 out of 659 (3.5%) COVID-19 patients with life-threatening pneumonia. In addition to the inborn monogenetic errors in *TLR3*, *IRF7*, and *IRF9* that have been reported as underlying life-

threatening influenza pneumonia, the same study identified LOF variants at another five genes involved in TLR3- and TLR7-dependent type I immunity. LOF variants were found in genes involved in TLR signaling to elicit type I IFN production (*TLR3*, *UNC93B1*, *TCAM1*, *TBK1*, and *IRF3*) and in type IFN-I signal amplification (*IRF7*, *IFNARI*, and *IFNAR2*; Fig. 4). Notably, these 23 patients had never been hospitalized for other life-threatening viral diseases. These data demonstrate not only the essential role of type I IFNs to control SARS-CoV-2 infection but also that inborn genetic disorders in type I IFNs are significant factors predisposing to severe illness. Moreover, X-linked LOF variants have also been identified in the *TLR7* gene of young male patients with fatal SARS-CoV-2 infection [111]. A recent genetic study of COVID-19 patients by GWAS approach also revealed low expression of *IFNAR2* associated with severe COVID-19 disease and identified IFN-inducible *Oligoadenylate synthetase (OAS)* as another COVID-19-linked gene [112]. Some of the IFN-I- and TLR3-associated genetic defects identified in COVID-19 patients with critical pneumonia are marked in Fig. 4.

Autoantibodies to type I IFNs impede the type I IFN response in COVID-19

The first indication that autoantibodies to type I IFNs might be a contributory factor to severe COVID-19 pneumonia was the observation of severe illness in APS-I patients, who are well known to carry autoantibodies to type I IFNs [113]. By screening for autoantibodies to type I IFNs in 987 patients with life-threatening COVID-19 pneumonia, Bastard *et al.* [8] observed that 101 (10.2%) of them had neutralizing anti-IFN- α and/or anti-IFN- ω autoantibodies. These autoantibodies were not observed in asymptomatic or mild SARS-CoV-2-infected individuals and were only found in 0.33% of healthy individuals. Typically, such autoantibodies are detected within 1–2 weeks after SARS-CoV-2 infection. However, identification of such autoantibodies in two patients before infection, together with nondetectable type I IFNs in the severe COVID-19 cases, suggests that these autoantibodies pre-existed in these patients and are a cause of the severe COVID-19 pneumonia rather than a consequence of SARS-CoV-2 infection. These autoantibodies impair the ability of IFN- α 2 to block SARS-CoV-2 infection in human cells *in vitro*, potentially explaining why SARS-CoV-2 infection is so severe in autoantibody-producing patients. These observations imply that IFN- α and IFN- ω are specifically critical in controlling

the pathogenesis of COVID-19-linked pneumonia. These autoantibodies to type I IFNs have only recently been identified and represent highly relevant factors predisposing individuals to severe SARS-CoV-2 infection. Understanding in detail the functions of type I IFNs in patients with these autoantibodies might provide important insights into the natural course of severe COVID-19 infection.

SARS-CoV-2 inhibits type I IFN production and responses

In addition to inborn mutation or autoantibodies, several studies have identified an attenuated expression of type I IFNs in COVID-19 patients. Dendritic cells taken from acutely infected patients present diminished production of IFN- α and IFN- β [114]. A systems biology analysis of severe COVID-19 patients showed reduced expression of IFN-I in their myeloid cells [115], which was accompanied by increased plasma levels of inflammatory molecules. Gene expression profiles of monocytes from COVID-19 patients with ARDS revealed deficient responses to IFN [116]. Notably, influenza patients do not show the attenuated type I/III IFN responses observed in COVID-19 patients [87,117]. Even though IL-6 plasma levels are elevated to similar levels in COVID-19 and influenza A virus-infected patients, SARS-CoV-2 infection induces IFN signaling (STAT1 and IRF3) in dendritic cells and T cells that is distinct from the signals (STAT3 and NF- κ B) activated by influenza A virus infection [117]. In a similar study, profoundly impaired production of IFN- λ and type I IFNs was found in COVID-19 patients, accompanied by highly elevated expression of pro-inflammatory cytokines, in contrast to uniformly produced type I and type III IFNs in patients with influenza [87]. These results suggest that SARS-CoV-2 selectively suppresses type I IFNs immediately upon infection [87,117–121].

Other CoVs, including SARS-CoV and MERS, are known to antagonize expression of type I/III IFNs and to attenuate their downstream signaling [111,122]. SARS-CoV delays early type I IFN expression in a mouse model of the virus, enabling higher viral titers, an accumulation of inflammatory monocyte–macrophages, vascular leakage, increased levels of lung cytokines, and attenuated virus-specific T-cell responses [123]. Depletion of inflammatory monocyte–macrophages rescued the mice from SARS-CoV-induced lethality, and early administration of IFN- β also prevented severe SARS-CoV-mediated disease. Type I IFNs also display a similar protective role in MERS [124].

SARS-CoV-2 inhibits production of type I IFNs and suppresses their signaling activity *in vitro*. It has been shown that NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6, and M proteins from SARS-CoV-2 inhibit IFN- β promoter activation, and ORF6 also inhibits ISRE and ISG56 promoter activation and suppresses STAT1 nuclear translocation [119]. In another study, ORF3b was shown to be a potent suppressor of type I IFN induction [125]. Similarly, ORF6, ORF8, and N proteins from SARS-CoV-2 suppress activation of the IFN- β and κ B promoters, with ORF6 and ORF8 further inhibiting the ISRE promoter [126]. Additionally, NSP13, NSP14, NSP15, and ORF6 attenuate production and signaling of type I IFNs [127]. SARS-CoV-2 suppresses type I IFN expression by its NSP16 protein-inhibiting mRNA splicing, its NSP1 protein-restricting mRNA translation, and NSP8/9 interfering with protein trafficking to the cell surface [128]. SARS-CoV-2 NSP3 protein (a papain-like PLpro protease) binds ISG15 and cleaves it from IRF3 to attenuate type I IFN responses [129]. NSP3 also directly cleaves IRF3 to suppress type I IFN signaling [130]. In addition, SARS-CoV-2 N protein binds retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA-5), molecular sensors of cytosolic double-stranded RNA, and the immediate signal protein mitochondrial antiviral signal (MAVS) and it inhibits the RIG-I/MDA-5-MAVS signal cascade [131,132]. Together, these results show that SARS-CoV-2 encodes several proteins inhibiting type I and type III IFNs, both at the expression and signaling level.

Link between early type I IFN deficiency and inflammation in severe COVID-19 cases

The afore-described results indicate that some severe COVID-19 patients are unable to mount an effective innate anti-SARS-CoV-2 response due to genetic defects in type I IFNs or they possess autoantibodies against type I IFN, whereas other patients with severe COVID-19 suffer from defective type I IFNs responses because they are suppressed by SARS-CoV-2. Figure 5 summarizes how deficiency in type I IFNs leads to excess inflammation in COVID-19. Type I IFNs attenuate inflammation during early viral infection, acting before inflammatory cytokines to minimize damage from inflammation [133]. In severe cases of COVID-19, expression of type I IFNs is attenuated and delayed, yet inflammatory cytokine and chemokine production is enhanced [87,118,121]. For patients with no IFN-I-associated IEs or anti-IFN-I antibodies, early administration of type I IFNs alleviates severe

COVID-19 disease [120,134–136], resulting in reduced viral load and decreased serum levels of IL-6 and C-reactive protein (CRP) [134,135]. These results indicate that the diminished early type I IFN responses contribute to subsequent hyperinflammation syndromes in patients with severe COVID-19 disease. The inability to control SARS-CoV-2 due to type I IFN insufficiency results in unrestricted viral replication, causing extensive tissue damage and cell death [89]. Uncontrolled viral replication leads to excess PAMPs for further inflammatory cytokine stimulation (Fig. 5). Among inflammatory cytokines, for example, high serum IL-6 levels predict poor COVID-19 prognosis [85,86]. The role of IL-6/STAT3 in severe COVID-19 is also implicated by that loss-of-function *STAT3* mutant protected against SARS-CoV-2 infection [10].

Similar to XLP-2, cell death likely plays a pivotal role in the transition to irreversible inflammation in severe COVID-19 [137,138]. Based on homology of SARS-CoV-2 ORF3a with that of SARS-CoV, the SARS-CoV ORF3a being a K⁺ channel, and ORF3-mediated K⁺ efflux enhancing NLRP3 inflammasome activation, SARS-CoV-2 is likely to activate inflammasomes [139]. This scenario was validated by active NLRP3 inflammasomes being found in the peripheral blood mononuclear cells of COVID-19 patients and in lung histology of COVID patients postmortem [140], supporting that SARS-CoV-2 infection induces pyroptosis [137,138]. Pyroptotic death has also been detected in the pneumocytes and endothelial cells of lung biopsies from COVID patients postmortem [89]. Importantly, high levels of TNF are always recorded in patients with severe COVID-19 [84,85,87,89], and TNF primes for necroptosis and apoptosis [137,138]. SARS-CoV-2 infection triggers caspase-8 activation, leading to apoptosis and necroptosis in a lung epithelial cell line [141]. Importantly, both monocytes and T lymphocytes from COVID-19 patients exhibit increased apoptotic signals [117], and pronounced apoptosis and necroptosis have been found in lung tissue from COVID-19 patients postmortem [89,141]. In addition, apoptotic gene signatures in plasmacytoid dendritic cells correlate with COVID-19 disease severity [142]. Moreover, inflammatory cell death arising from pyroptosis, apoptosis, and necroptosis (termed PANoptosis) can be induced by a combination of TNF and IFN- γ [58], and this is likely key to the pathogenesis of COVID-19. Therefore, in the absence of early type I IFNs to repress SARS-CoV-2 replication, SARS-CoV-2 triggers extensive cell death. SARS-CoV-2-mediated cell death and inflammatory cell death together enhance the release of DAMPs that further stimulate innate receptors for more inflammatory

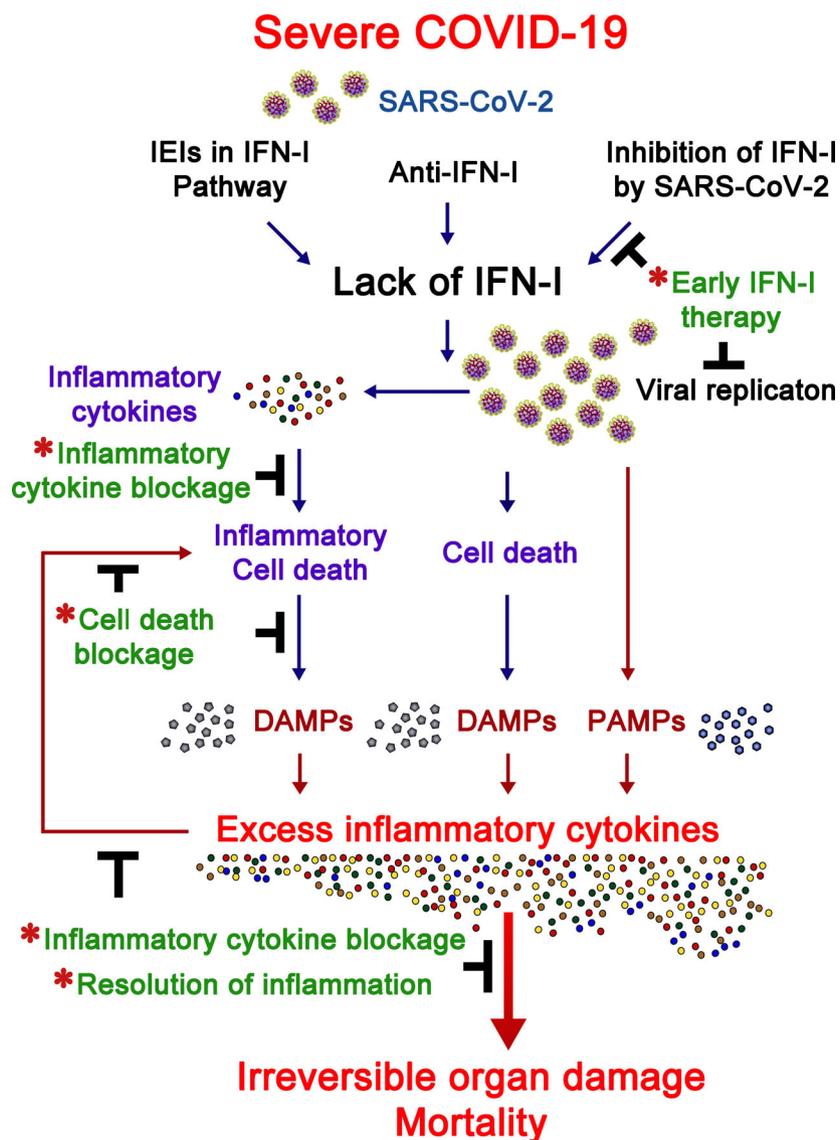


Fig. 5. Infection-induced inflammation in COVID-19. Type I IFNs are critical to early control of SARS-CoV-2 infection. A small proportion of patients with severe COVID-19 bear IEI of type I IFN pathway genes. Other such patients carry anti-IFN-I antibodies, and SARS-CoV-2 suppresses the expression of type I IFNs and their downstream signaling molecules in other severe COVID-19 cases. Deficiency in type I IFN cascades leads to unrestricted viral replication and enhanced inflammatory cytokine production. PAMPs arising from SARS-CoV-2 infection, DAMPs from cell death induced by viral replication, and DAMPs from inflammatory cell death activated by inflammatory cytokines trigger excess inflammatory cytokine production that, in turn, induce more inflammatory cell death. This scenario may lead to irreversible organ damage and patient mortality. Infection-induced inflammation in COVID-19 may be alleviated (marked by *) by early type I IFN administration, inflammatory cytokine blockage, inflammatory cell death blockage, or resolution of inflammation. For details of each therapeutic approach, refer to the text.

cytokine production, in turn inducing even more inflammatory cell death (Fig. 5). The extensive inflammation and cell death associated with SARS-CoV-2 may lead to the irreversible organ damage and mortality linked to COVID-19. Thus, infection-induced inflammation and cell death play dominant roles in the pathogenesis of COVID-19, resulting in irreversible organ damage and even mortality.

Therapeutic implications for COVID-19

Figure 5 also marks the potential therapeutic approaches to COVID-19 intervention. First, it is necessary to screen for IFN-I-associated IEIs and the presence of anti-IFN-I antibodies in severe COVID-19 patients. Such screening will enable provision of

specialized clinical care to respective COVID-19 patients, potentially slowing disease progression. Despite the narrow sensitivity to viral infection for each monogenic IEI defect, extension of screening to genes encoding proteins required for responses to other viruses, such as SH2D1A, XIAP, ITK, NOS2, and DBR1, could also be helpful in COVID-19 patient assessments [7].

For patients lacking IFN-I-associated IEIs or anti-IFN-I autoantibodies, SARS-CoV-2 suppresses the early production of type I IFNs that leads to pathogenesis. The low levels of such IFNs in patients with severe COVID-19 and consequently elevated inflammation imply that type I IFN administration is a potential treatment for COVID-19. Initial clinical studies support the efficacy of such treatment. Early IFN- α or

IFN- β administration improves clinical outcomes, increases viral clearance, decreases in-hospital COVID-19 deaths, and enables more rapid recovery [120,134–136]. Notably, IFN-I treatment should be beneficial for the COVID-19-infected IEI patients who cannot mount IFN-I production. Indeed, the IFN- α 2b treatment showed a clinical benefit for two COVID-19 patients with TLR3 or IRF3 mutation [143]. Importantly, even in COVID-19 patient with autoantibodies against IFN- α and IFN- ω treatment with IFN- β is shown to resolve syndromes [144], supporting the therapeutic application of IFN- β in patients bearing anti-IFN- α /IFN- ω autoantibodies. However, the timing of early type I IFN administration is critical in treating COVID-19. In mouse infection models of SARS-CoV and MERS, delayed IFN- β treatment exacerbated disease, resulting in increased infiltration and activation of myeloid cells in lung tissues and elevated inflammatory cytokines, leading to fatal pneumonia [123,124]. Similar outcomes have been reported for COVID-19 cases, in which late IFN- α 2b treatment delayed recovery and increased mortality [120].

High levels of inflammatory cytokines have been implicated in contributing to severe cases of COVID-19, so various anticytokine monoclonal antibodies have been subjected to clinical trials to determine their suitability for treating severe COVID-19-linked pneumonia. Even though there is discrepancy on the efficacy of IL-6 neutralization [145], recent clinical trials found that anti-IL-6R improves clinical outcomes and survival in both moderately and critically ill COVID-19 patients [146,147]. Preliminary results also suggest that other inflammatory cytokines may represent promising targets. Monoclonal antibodies to GM-CSF receptor showed a promising therapeutic effect for COVID-19 pneumonia in clinical trial [148], reflecting the likely role of macrophage overactivation in severe COVID-19 infection. A beneficial effect of anti-TNF in COVID-19 therapy has been suggested [149], which warrants further characterization. Tests on anti-IFN- γ (NCT04324021) monoclonal antibodies are ongoing [150]. In addition, monitoring the natural course of SARS-CoV-2 infection in patients with natural autoantibodies to IFN- γ and GM-CSF might provide important data informing the design of such treatments.

Persistent infection-induced inflammation is a shared feature of COVID-19 and XLP-2. Though caused by different viruses (EBV versus SARS-CoV-2) and the clinical syndromes of COVID-19 being distinct from the HLH of XLP-2 [151,152], inflammatory cell death likely represents a turning point from infection to irreversible inflammation in both COVID-19 and XLP-2.

Inhibition of inflammatory cell death triggered by a combination of anti-TNF and anti-IFN- γ significantly rescued SARS-CoV-2-induced mortality in a COVID-19 mouse model [58], suggesting a potential application in the treatment of COVID-19 patients.

Alternatively, tackling inflammation may help control infection-induced pathologies in IEIs, and it is likely to be effective in COVID-19 therapy. One well-known example of a respective therapy is dexamethasone, which acts by reducing inflammation, and it has been approved for use to improve disease status and to reduce the mortality associated with moderately and severely ill COVID-19 patients [153,154]. Recent study of a rhesus macaque COVID-19 model has also shown that treatment with baricitinib, a JAK1/JAK2 inhibitor, resolves lung inflammation by suppressing the production of inflammatory cytokines by macrophages and by inhibiting neutrophil recruitment, without affecting type I IFN signaling [155]. Early clinical trial results of baricitinib, by itself or in combination with remdesivir, on hospitalized COVID-19 patients, showed reduced inflammation and favorable clinical outcomes [156,157], supporting the efficacy of JAK1/JAK2 inhibitors in resolving SARS-CoV-2 infection-induced inflammation. From observations of IEIs in a XLP-2 mouse model, infection-induced inflammation and mortality can be prevented by using resolvin D or *ex vivo*-expanded Tregs without the need for antimicrobial agents [33,34], suggesting that similar approaches could be tested for their efficacy in controlling the persistent inflammation associated with COVID-19. Mesenchymal stem cells, characterized by their anti-inflammatory activities and Treg-inducing capacity, have also been used in a small number of COVID-19 patients, and respective clinical trials are ongoing [158].

Altogether, a variety of therapeutic approaches targeted to several steps contributing to the persistent inflammation of COVID-19 are currently being investigated. These pathways are distinct from the processes exerted by antiviral reagents, such as blocking viral entry by anti-SARS-CoV-2 antibodies or inhibiting viral replication via small-molecule antiviral drugs, so the inflammation-targeting therapies are completely independent of antiviral treatments. Based on the prominent role of persistent inflammation in COVID-19 pathogenesis, resolving inflammation is likely to be as effective as antiviral therapy at treating COVID-19 patients.

Conclusion

In this review, we have explored the pathogenic mechanisms underlying specific IEIs and COVID-19. Anti-

IFN-I antibodies and IFN-I-associated IEIs are found in patients with severe COVID-19. Anticytokine autoantibodies were first identified many years ago, and they have been found to cause various diseases, including autoimmune and infectious diseases. However, the importance of late-onset immunodeficiency remains underestimated, in particular for infectious diseases. The COVID-19 pandemic has had an unparalleled impact, but it is also presenting an opportunity to better understand the roles of anticytokine autoantibodies in infectious diseases. Thus, investigations of anticytokine autoantibodies against type I IFNs and even other cytokines are warranted in patients with SARS-CoV-2 infection, and indeed other infections, to establish which host factors predispose to infectious diseases. Careful dissection of clinical manifestations and physiological responses during infectious, autoimmune, and other diseases, including COVID-19, in patients having anticytokine autoantibodies, will help develop new diagnoses and treatments.

For COVID-19 patients harboring inborn mutations in type I IFN signaling pathways or with autoantibodies against type I IFNs, they represent the latest examples that genetic mutation or phenocopies of IEI exacerbate infection-induced ARDS. For other patients without apparent genetic deficiency, COVID-19 may be reminiscent of immunodeficiency diseases in which early type I IFN responses are suppressed, leading to an eventual breakout of inflammation. This feature of persistent infection-induced inflammation is shared by IEIs such as XLP-2. Cell death most likely largely accounts for the transition from persistent viral infection to inflammation in both IEIs and COVID-19. Inhibition of cell death and resolving persistent inflammation thus represent potential approaches for tackling IEIs and COVID-19. Several agents based on such mechanisms and undergoing clinical trials are highly promising COVID-19 therapies, including early administration of type I IFNs, use of anti-TNF and/or anti-IFN- γ antibodies, or application of JAK1 or STAT1 inhibitors. Importantly, alleviation of infection-induced inflammation should be conducted synergistically with antiviral treatments to achieve optimal therapeutic effects in COVID-19 patients. Overall, SARS-CoV-2 infection-induced inflammation is a primary cause of COVID-19 pathogenesis and so it should be a primary target for COVID-19 therapies.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

C-LK and M-ZL conducted a literature search and wrote the manuscript; I-TC designed and prepared the figures.

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