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SARS-CoV-2 infection is benign in most individuals but, in ~10% of cases, it triggers hypoxemic COVID-19 pneumonia, which becomes critical in ~3% of cases. The ensuing risk of death (~1%) doubles every five years from childhood onward and is ~1.5 times greater in men than in women. What are the molecular and cellular determinants of critical COVID-19 pneumonia? Inborn errors of type I IFNs, including autosomal TLR3 and X-linked TLR7 deficiencies, are found in ~1-5% of patients with critical pneumonia under 60 years old, and a lower proportion in older patients. Pre-existing autoantibodies neutralizing IFN-α, −β, and/or −ω, which are more common in men than in women, are found in ~15-20% of patients with critical pneumonia over 70 years old, and a lower proportion in younger patients. Thus, at least 15% of cases of critical COVID-19 pneumonia can apparently be explained. The TLR3- and TLR7-dependent production of type I IFNs by respiratory epithelial cells and plasmacytoid dendritic cells, respectively, is essential for host defense against SARS-CoV-2. In ways that can depend on age and sex, insufficient type I IFN immunity in the respiratory tract during the first few days of infection may account for the spread of the virus, leading to pulmonary and systemic inflammation.

More than 5 million people have died from COVID-19, and infection fatality rates (IFR) in unvaccinated populations are ~1%[1,2]. Indeed, infection with SARS-CoV-2 is silent in ~40% of cases, underlies a benign upper respiratory tract disease in another 40%, and causes pneumonia in ~20%[3,4]. Non-hypoxemic, 'moderate' pneumonia is seen in ~10% of cases, whereas the remaining 10% of cases present hypoxemic pneumonia, typically requiring hospitalization for oxygen therapy. In ~3% of cases, the administration of O_2 at a rate < 6 L/min (the cutoff for 'severe' pneumonia) is not sufficient to alleviate hypoxemia. In such cases, high-flow oxygen (O_2 > 6 L/min), mechanical ventilation (non-invasive or by intubation), or extracorporeal membrane oxygenation (ECMO) is required (any of these three options, typically provided in intensive care units, defines 'critical pneumonia')[5,6]. The IFR increases exponentially with age, doubling every five years, from 0.001% in individuals aged 5-9 years to 8.29% in those over the age of 80 years[1,7–10]. Ancestry, social status, and several comorbid conditions have been associated with higher disease severity and death rates, but with modest odds ratios (OR, typically <1.5, rarely >2)[7–9]. Men have a 1.5 times greater risk of death than women, after adjustment for other risk factors[1,11]. Overall, the striking epidemiological feature of life-threatening COVID-19 is its strong dependence on age, steadily increasing throughout life, with a 10,000 times greater risk at ages > 80 years than in the first decade of life[1,12,13]. A similar pattern is seen with the more transmissible viral variants[14,15]. The same viruses are found in patients with silent and lethal infections, excluding the hypothesis that interindividual clinical variability is primarily a consequence of viral diversity.

The hypothesis that a large amount of viral inoculum is more life-threatening than a small inoculum is more plausible, in line with the findings of 100 years of experimental inoculations of animals with pathogens[16]. However, it is difficult to test this hypothesis in humans. One alternative hypothesis is that humans with life-threatening COVID-19 were particularly prone to critical illness due to an underlying and hitherto silent immunodeficiency[17,18]. The traditional view of immunodeficiency, characterized by overt immunological abnormalities and broad vulnerability to infectious agents — as illustrated by patients with acquired immunodeficiency syndrome or severe combined immunodeficiency, who lack T cells due to HIV infection and germline mutations, respectively — has turned out to be the tip of an iceberg. Since 1996, previously healthy patients with rare or common infectious diseases but normal resistance to other infectious agents have been found to carry inborn errors of immunity (IEIs) rendering them particularly susceptible to specific microbes. Rare IEIs have been implicated in at least 20 different types of viral, bacterial, fungal, and parasitic infections[17,18]. These rare IEIs led to the discovery of a common IEI, accounting for about 1% of cases of tuberculosis in populations of European descent[19,20]. Based on all these findings, we launched the COVID Human

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Genetic Effort (CHGE, www.covidhge.com) with the aim of discovering the molecular, cellular, and immunological determinants of the various SARS-CoV-2-related manifestations by searching for causal IEIs[13]. We review here these and other studies that have clarified the human genetic and immunological determinants of life-threatening COVID-19 pneumonia[12,13,21–24]. We do not consider other phenotypes, such as resistance to infection[25], pernio ("COVID toes")[26], multisystem inflammatory syndrome in children or adults (MIS-C/A)[27], neuro-COVID[28], or long COVID[10,29], for which genetic and immunological studies have only just begun.

Inborn errors underlying critical influenza

The first breakthrough emerged from a study of candidate inborn errors of TLR3-, IRF7-, and IRF9-dependent type I IFN immunity that had previously been shown to underlie life-threatening influenza pneumonia (Figure 1)[5,17,18,24,30–32]. Predispositions to critical COVID-19 and influenza were hypothesized to be allelic because both conditions are respiratory infections caused by RNA viruses[12]. The first influenza susceptibility gene discovered encodes IRF7, the inducible transcription factor responsible for amplifying type I IFN production in virus-infected cells[33]. Plasmacytoid dendritic cells (pDCs) constitutively express high levels of IRF7 and are the most potent producers of type I IFN[34,35]. The second encodes IRF9, the DNA-binding component of the interferon-stimulated gene factor 3 (ISGF-3) complex activated by type I and III IFNs[36]. The third encodes TLR3, an endosomal dsRNA sensor that regulates basal levels of type I IFN in various non-hematopoietic cells[37], possibly including respiratory epithelial cells (RECs)[24,32]. Germline mutations at these three human loci are causal for critical influenza pneumonia[30–32]. We also considered 10 other genes, the products of which are biochemically and immunologically connected to these three core genes (Figure 1), and for which deleterious genotypes have been shown to underlie other severe viral diseases (suggesting incomplete penetrance for influenza)[5]. These 13 loci encode proteins for which a genetic deficiency can be considered to confer a high risk of critical influenza.

Autosomal inborn errors of type I IFNs

Biochemically deleterious germline mutations of eight of the 13 genes were found in 23 of 659 patients with critical COVID-19 (3.5%) aged 17 to 77 years, including 18 patients under 60 years old (3.8%). Remarkably, four unrelated previously healthy adults, aged 26 to 50 years, had autosomal recessive (AR) complete IRF7 or IFNAR1 deficiency. The other patients had known (*n*=11) or previously unreported (*n*=8) autosomal dominant (AD), partial deficiencies. None of these patients had ever been hospitalized for other viral infections, including influenza. The penetrance of these disorders for critical COVID-19 is also probably incomplete, but higher for the AR than for the AD disorders, and for the known than for the unreported AD disorders (Table 1). A 13-year-old boy with AR IFNAR1 deficiency[38] and a three-year old girl with AR TBK1 deficiency[39] were independently reported to have critical COVID-19[40]. Fibroblasts presenting AD or AR TLR3 deficiency, AR IRF7 deficiency, or AR IFNAR1 deficiency displayed defective type I IFN-dependent control of SARS-CoV-2 *in vitro*[5], suggesting that RECs may display the same phenotype[32]. Moreover, pDCs from an IRF7-deficient patient were unable to induce type I IFNs upon stimulation with SARS-CoV-2 *in vitro*. This experimental approach provided proof-of-concept that IEIs affecting type I IFNs, including disorders of TLR3-dependent type I IFN immunity in RECs, and even AR defects that blunt type I IFN immunity across cell types, can underlie life-threatening COVID-19 pneumonia in previously healthy patients[12,21] (Figure 1).

X-linked recessive TLR7 deficiency

In parallel, an X chromosome-wide approach resulted in the discovery of X-linked recessive (XR) TLR7 deficiency, a previously unknown IEI[41]. In a cohort of 1,202 unrelated male patients with critical pneumonia, 17 patients (1.4%) from 16 kindreds were hemizygous for biochemically deleterious *TLR7* variants, whereas none of the 331 men with asymptomatic or mild COVID-19 carried such mutations[41]. Sixteen of the 17 patients are below the age of 60 years (1.8%). One of these patients also had ataxia-telangiectasia (AT), which was not causal for critical COVID-19 in other patients with AT infected with SARS-CoV-2[42]. TLR7 deficiency was also found in 1% of patients with severe, but not critical COVID-19 (i.e. with O_2 < 6 L/min). The penetrance of XR TLR7 deficiency for severe or critical COVID-19 among relatives of index cases was high, but incomplete, especially in children (Table 1). We also found that the cumulative minor allele frequency (MAF) of deleterious alleles in men was < $6.5x10^{-4}$. Moreover, six of the 11 *TLR7* variants previously reported in other patients were deleterious (carried by 9 of 16 patients)[43–46], whereas the variants in another study were not disclosed[47]. We further showed that the *TLR7* genotype was deleterious in patients' EBV-transformed B (EBV-B) cell lines. Overall, these genetic and biochemical data implicated XR TLR7 deficiency due to deleterious variants in at least 1% of critical cases of COVID-19 in male patients under the age of 60 years, with high penetrance.

Deficiency of plasmacytoid dendritic cells

TLR7-deficient pDCs did not respond to the TLR7-specific agonists tested. Moreover, when challenged with SARS-CoV-2 *in vitro*, they displayed severely impaired, but not entirely absent type I IFN induction[41]. TLR9 is probably responsible for the residual response, as UNC-93B- and IRAK4-deficient pDCs do not respond at all to the virus[48] (Figure 1). The discovery of XR TLR7 deficiency through an unbiased approach thus confirmed the key role of type I IFN immunity in protection against SARS-CoV-2 in the respiratory tract[41]. It also suggested that pDCs are essential for this process. It has long been known that pDCs are the most potent discernible type I IFN-producing cell type[34,49–51]; this experiment of nature suggests that these cells are essential for antiviral immunity, as the other TLR7-expressing myeloid and lymphoid cells are poor producers of type I IFNs[52]. Human TLR7 is now firmly established as a key player in host defense. The activation of TLR7 by viral RNA was long known[53–57], with its gene shown to be subject to strong negative selection in the general population[58], but its role in host defense had remained elusive, as patients with deficiencies of MYD88 or IRAK4 displayed no severe viral illnesses and the viral infections observed in UNC-93B-deficient patients had been attributed to their TLR3 pathway defects[59]. Overall, TLR3-dependent type I immunity in RECs and TLR7-dependent type I IFN immunity in pDCs appear to be strong determinants of protection against SARS-CoV-2 in the respiratory tract.

Other inborn errors of type I IFN immunity

Nine IEIs of type I IFN immunity were thus found to underlie life-threatening COVID-19 with low (AD disorders) or high (AR, XR) penetrance. In addition, five young patients with related IEIs – MYD88[60], IRAK4[61], and GATA2 deficiencies[62,63] – were hospitalized, for COVID-19 pneumonia, albeit of moderate severity. Severe influenza infections had been reported in patients with GATA2 deficiency, probably caused at least partly by low counts of circulating pDCs[64], which do not require TLR7 to sense influenza virus[30,48]. Other patients with MYD88, IRAK4, or GATA2 deficiency are probably susceptible to hypoxemic COVID-19 pneumonia[48]. Defects of other genes involved in type I IFN immunity may also increase susceptibility to COVID-19 (Figure 1). Overall, the nine IEIs of type I IFN immunity identified may already account for about 1-5% of life-threatening cases of COVID-19, especially among patients under 60 years old, with XR TLR7 deficiency alone accounting for over 1% of critical cases in men. This proportion is high, exceeding the 1% of cases of tuberculosis in Europeans for which a genetic explanation has been obtained, for example[19,20]. Other causal IEIs affecting type I IFN

will probably be discovered in the future. Indeed, AR IFNAR1 and IRF7 deficiencies have already acted like a compass, pointing us in the right direction for the discovery of a more common cause of life-threatening COVID-19.

From inborn errors to their phenocopy

Auto-Abs against type I IFNs were first detected in the 1980s, in patients treated with type I IFN or with systemic lupus erythematosus (SLE)[65–67]. Their production can be genetically driven, as in patients with autoimmune polyendocrine syndrome type-1 (APS-1) due to germline mutations of *AIRE*, which controls the thymic expression of peripheral self-antigens and, thus, central T-cell tolerance[68–70]. They are also found in men with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) due to mutations of *FOXP3*, encoding a protein that governs the development of regulatory T cells and thus, peripheral T-cell tolerance[71,72], and in patients with combined T/B cell immunodeficiency due to hypomorphic mutations of *RAG1* or *RAG2*[73]. Auto-Abs against type I IFN may also be produced in two overlapping conditions[74] of elusive etiology: thymoma[75] and myasthenia gravis[76,77]. Patients with APS-1 and thymoma have thymic epithelial-intrinsic defects, whereas patients with *RAG1*/*RAG2* and *FOXP3* mutations have T cell-intrinsic defects[70,78,79]. These auto-Abs have been widely recognized for 40 years, and were even reported in an otherwise healthy patients with severe varicella zoster virus (VZV) infection by Ion Gresser as early as 1984[80], but they were not thought to confer a predisposition to viral diseases. By contrast, autoimmune phenocopies of IEIs disrupting type II IFN (IFN-γ), IL-6, IL-17A/F, and granulocyte-macrophage colony-stimulating factor (GM-CSF), have long been known to underlie mycobacterial disease, staphylococcal disease, mucocutaneous candidiasis, and nocardiosis, respectively[18,81–88].

Autoantibodies neutralizing type I IFNs

We found that at least 10% of individuals with critical COVID-19 had auto-Abs neutralizing supraphysiological concentrations (10 ng/mL, in plasma diluted 1/10) of IFN-α2 and/or IFN-ω[6]. These findings were widely replicated[89–102]. In our and another study, these auto-Abs were not found in patients with silent or benign SARS-CoV-2 infections[6,92]. Alarmingly, auto-Abs neutralizing type I IFN were found in therapeutic convalescent plasma from a few patients hospitalized for COVID-19[99]. In the few patients tested, the auto-Abs pre-existed SARS-CoV-2 infection. Moreover, APS-1 patients, who produce such auto-Abs from early childhood, were at very high risk of developing severe or critical COVID-19 pneumonia, especially in patients over 20 years old[103,104]. An elegant unbiased study reported that a number of patients with hypoxemic COVID-19 pneumonia displayed diverse auto-Abs[92], most of which were probably triggered by SARS-CoV-2 infection and may have influenced the course of disease. This and a longitudinal study of a small group of patients suggested that SARS-CoV-2 infection might boost the levels of pre-existing type I IFN auto-Abs[105]. The auto-Abs blocked the protective effect of IFN-α2 against SARS-CoV-2 *in vitro*[6]. Furthermore, circulating IFN-α concentrations were low or undetectable *in vivo* in patients with auto-Abs against IFN-α2, which also target the 13 forms of IFN-α[6]. These auto-Abs also impair type I IFN activity in peripheral blood mononuclear cells[93]. Impaired expression of IFN-stimulated genes (ISGs) was also observed in the respiratory tract in patients with auto-Abs[96,106] (Figure 2). Indeed, these auto-Abs were also detected in tracheal aspirates and nasal swabs[106,107].

Neutralization of lower concentrations

The physiological concentrations of IFN-α in the blood during SARS-CoV-2 infection are much lower (between 1 and 100 pg/mL in undiluted plasma)[108] than the concentrations used in our initial experiments (10 ng/mL in plasma diluted 1/10). We found that ~14% of patients with critical COVID-19 pneumonia had auto-Abs neutralizing lower, more physiological, concentrations of IFN-α and/or IFN-ω (100 pg/mL in plasma diluted 1/10)[109]. The proportion of such patients increased after the age of 65 years and was greater in men than in women. In addition, another ~1% of patients had auto-Abs neutralizing 10 ng/mL IFN-β only. Globally, ~20% of patients with critical COVID-19 over 80 years of age, and ~20% of deceased patients across all ages, had these auto-Abs. Moreover, ~7% of patients with severe, but not critical, COVID-19 had these auto-Abs, too. We estimated ORs by comparing the prevalence of auto-Abs in patients with critical disease with that in patients with asymptomatic or mild infection[109] (Table 1). For most categories of auto-Abs to type I IFN, their prevalence was not null in patients with silent or mild infection, as previously documented for patients with APS-1[103,104]. The highest ORs were obtained for auto-Abs neutralizing both IFN-α and IFN-ω at concentrations of 10 ng/mL or 100 pg/mL, followed by auto-Abs against IFN-α only, whereas the ORs for auto-Abs against IFN-ω only were lower. For auto-Abs against IFN-β only, the ORs for critical disease were even lower. Remarkably, however, auto-Abs neutralizing only IFN-β can underlie life-threatening COVID-19, as can auto-Abs against IFN-α only or IFN-ω only[6,109].

Autoantibodies in the general population

We tested more than 34,000 individuals from the general population aged 18 to 100 years. We found that the prevalence of auto-Abs neutralizing 10 ng/mL (or 100 pg/mL) IFN-α or IFN-ω was not only higher in men than in women, but also increased significantly with age in the general population, with 0.17% (1.1%) of individuals positive for these antibodies before the age of 70 years, and more than 1.4% (4.4%) positive after the age of 70 years[109]. This striking distribution probably contributes to the higher risk of death from COVID-19 in the elderly population. Interestingly, auto-Abs neutralizing IFN-α and/or IFN-ω are much more prevalent in the elderly population, whereas auto-Abs neutralizing IFN-β seem to have a similar prevalence in all age groups tested. IFN-ω and the 13 forms of IFN-α are very similar biochemically, closely related phylogenetically, and found in the blood, whereas IFN-β, IFN-ε, and IFN-κ differ structurally and functionally. IFN-β is widely required to initiate the production of other type I IFNs, whereas IFN-ε and IFN-κ are predominantly expressed in reproductive and cutaneous tissues (and not tested in our studies of auto-Abs)[110–112]. Defective activity for all 13 IFN-α, or IFN-ω, or IFN-β, or a combination of these molecules may remain silent for long periods, until a virus, such as SARS-CoV-2, reveals the deficiency[112–114]. Overall, auto-Abs to type I IFNs appear to be strong determinants of critical COVID-19 pneumonia.

Clinical implications

Auto-Abs neutralizing type I IFNs apparently underlie already almost one million deaths from COVID-19 worldwide (15-20%). These studies thus have clinical implications, because (i) it is straightforward to test for these neutralizing auto-Abs before infection, (ii) individuals with these antibodies should be vaccinated early and given priority for booster injections, (iii) it is also possible to test for these antibodies during the early stages of COVID-19, (iv) specific treatments, such as IFN-β, mAbs neutralizing SARS-CoV-2, or plasma exchange could then be considered and tested in unvaccinated, and perhaps even in vaccinated individuals[115,116]. Finally, these auto-Abs against type I IFNs also underlie severe adverse reactions to vaccination with the live attenuated virus vaccine against yellow fever and perhaps other viral infections[80,117,118]. Together with IEIs of type I IFN immunity, these findings may explain the pathogenesis of about 15-20% of cases of critical COVID-19 pneumonia, especially in patients over 70 years old (Table 1, Figure 3). We know from IPEX[71], RAG1/2 deficiencies[73], incontinentia pigmenti[6,119], and APS-1[103–105,120,121] that some IEIs can underlie the production of auto-Abs

against type I IFNs. It will be interesting to determine whether other IEIs also underlie the production of auto-Abs against type I IFN[63,122–124]. It will also be interesting to elucidate the reasons for the sudden increase in these auto-Abs after 65 years of age, especially in men.

Type I IFNs in unexplained COVID-19

Before the discovery that type I IFN deficiency may underlie critical COVID-19 in some patients, some observations suggested that type I IFN levels in the blood of a subset of patients with critical COVID-19 pneumonia were lower than for other forms of infection[108,125–127]. By contrast, other studies reported enhanced type I IFN activity in a subset of patients with critical COVID-19[128–130]. Studies on patients with no known determinant of critical disease are, by nature, inconclusive. At best, the abnormalities detected can be correlated with disease severity, but it remains unclear whether they are a cause or consequence of disease. In the infinite and multidimensional matrix of causes and consequences, involving countless viruses and cell types, in individual patients, each of whom is unique, from the first day of infection to the death of the patient or viral clearance, it is difficult to establish a causal relationship. This has always been a fundamental problem in the field of infectious diseases, and in medicine at large, and has resulted in observational studies in humans gradually being replaced by experimental studies of cells *in vitro* and of animals *in vivo*, and, more recently, by the study of the human genetic determinants of infectious diseases[17,18,24]. The discovery of genetic lesions or pre-existing auto-Abs has provided an anchor on which observations of COVID-19 or other infections can be fixed to establish causality.

Type I IFN biology in patients with deficiencies

Only one patient with a type I IFN IEI, AR IRF9 deficiency, has been studied immunologically, early in the course of infection[131]. The impact of auto-Abs on systemic and/or mucosal immunity has been studied by scRNAseq in more patients[93,96]. These studies showed that critically ill patients had weaker ISG responses in myeloid cells, this lack of responsiveness being particularly marked in patients with auto-Abs against type I IFN[93]. Consistently, scRNAseq on nasopharyngeal swabs showed that patients with critical COVID-19, including one patient with auto-Abs against type I IFNs, had muted ISG responses[96]. Finally, auto-Abs against type I IFN have been detected in nasal fluids, and nasal ISG responses have been shown to be correlated with nasal viral load, systematic ISG responses in leukocytes, and blood type I IFNα levels[106]. The patients with auto-Abs against type I IFN and critical COVID-19 tested also displayed increases in the levels of inflammatory cytokines in both the respiratory tract and the blood, suggesting a two-step-model for the pathogenesis of critical COVID-19, with insufficient type I IFN in the first few days of infection unleashing excessive inflammation from the second week onward[12]. Overall, these extensive studies have suggested that patients with critical COVID-19 and auto-Abs against type I IFN have insufficient systemic and nasal type I IFN activity early in the course of disease (Figure 2).

Other inborn errors of immunity

What have we learned from the study of patients with IEIs that do not impair type I IFN immunity directly or via the production of auto-Abs? In 10 retrospective cohorts of patients with various IEIs, the natural history of SARS-CoV-2 infection seemed to resemble that in the general population, albeit apparently with higher mortality in some IEI subsets[61,63,123,124,132–137]. A prospective study of IEI patients reached similar conclusions[60]. Interestingly, patients with predominant antibody deficiencies are not prone to life-threatening COVID-19 pneumonia[61,63,123,124,132–137]. This is consistent with the findings for critical influenza pneumonia, which is specifically seen in patients with IEIs of type I IFN immunity, but not in other individuals, even those lacking T and/or B cells[64]. Patients with IEIs of T and/or B cells may suffer from chronic COVID-19 infection and prolonged viral shedding[138–141], like patients with acquired adaptive immunodeficiencies[142–144]. Multi-mutated, potentially more pathogenic SARS-CoV-2 variants might arise in such cases of persistent infection[138]. No IEIs other than those impairing type I IFN immunity directly or via auto-Abs have been genetically or mechanistically associated with life-threatening COVID-19, but their vast genetic and immunological heterogeneity, and their individual rarity suggest that targeted clinical surveys are warranted. In particular, type I and III IFNs both activate ISGF-3 and induce a largely overlapping range of ISGs[64,112] (Figure 1). It would be interesting to study the course of SARS-CoV-2 infection in patients with AR IL-10RB deficiency, whose cells respond to type I but not type III IFNs (Figure 1).

Genome-wide association studies

The key result of genome-wide association studies (GWAS) is the identification of common variants of chromosomal region 3p21.31 associated with critical COVID-19[145–148]. The risk haplotype, inherited from Neanderthals, confers an estimated OR per copy of between 1.6 and 2.1, with higher values for individuals under 60 years old[148–150]. The region encompasses six genes, including *CXCR6* and *LZTFL1*. Five other genome-wide regions have been shown to be significantly associated with critical COVID-19[147]. Three of these regions encompass genes involved in type I IFN immunity. The first, on chr12q24.13, containing protective variants inherited from Neanderthals, includes the *OAS1*, *OAS2*, and *OAS3* cluster, ISGs required for the activation of anti-viral RNaseL[151]. The second, a region on chr21q22.1, includes *IFNAR2*. The third, a region on chr19p13.2, includes *TYK2*. In these regions, one copy of the risk allele increases the risk of critical COVID-19 slightly, with ORs below 1.5. An OR of 1.5 is often presented as increasing the risk by "50%", but, assuming that the OR does not overestimate the relative risk, the mathematical and clinical reality is that, for a COVID-19 mortality risk of 0.006% at the age of 20 years, 0.2% at the age of 50 years, and 8.3% at the age of 80 years[1], individuals carrying the at-risk genotype have risks of 0.009%, 0.3%, and 12.5%, respectively. Although modest at the individual level, the impact of these findings is significant at the population level (Table 1)[152]. These studies may not only reveal genetic modifiers of stronger determinants of disease, but also mechanisms that are type I IFN-dependent or -independent.

Genome-wide search for rare variants

In a population-based exome-wide association study[47] using a relaxed Bonferroni threshold ($p<5x10^{-8}$), the authors identified eight genes, one of which, *TLR7*, displayed an enrichment in pLOF and in-frame variants with a MAF $< 10^{-5}$ in critically ill COVID-19 patients relative to individuals of unknown or seronegative status for SARS-CoV-2 infection. By contrast, this study and a previous rare-variant candidate gene association study[153] reported no enrichment in pLOF variants of 13 type I IFN-related influenza susceptibility genes[5] in patients with critical COVID-19 pneumonia. Two possible reasons for this apparent discrepancy are of particular importance[154]. First, age, the key epidemiological factor driving COVID-19 severity was ignored. Our cohort was much younger (mean age of 52 vs. 66 years) and these IEIs are more frequent in patients under the age of 60 years[154]. Second, no tests were performed for auto-Abs against type I IFN, the most common known determinant of critical COVID-19, especially in patients over 60 years old[154]. More importantly, the proportions of patients with critical COVID-19 due to AR, XR, and AD IEIs at these (or other) loci may vary from population to population. Finally, their causal link to critical COVID-19 cannot be concluded or excluded from an enrichment analysis of untested variants: it should be based on biochemical, virological, and immunological experiments mechanistically connecting germline genotypes with clinical phenotypes[5,40–42].

SARS-CoV-2 interference with type I IFN

The discovery that insufficient type I IFN can underlie critical COVID-19 pneumonia *in vivo* is remarkably convergent with various elegant virological studies conducted in human cells *in vitro*. Indeed, SARS-CoV-2 induces type I IFN production less strongly than seasonal influenza A viruses (IAV)[155] or Sendai virus (SeV)[156]. The ability of SARS-CoV-2 to evade type I IFN induction results not only from the non-specific inhibition of host cellular functions, such as transcription and translation[157–159], but also from the specific suppression of type I IFN induction pathways. Despite the limitations of overexpression systems, numerous studies have shown that at least 14 of the 31 products of known open reading frames (ORFs) of SARS-CoV-2 (Nsp1, Nsp5, Nsp6, Nsp13, Nsp14, Nsp15, ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF9b, M, and N) target host proteins governing type I IFN induction, including IRF3, TBK1, MAVS, RIG-I, and NEMO, or self-amplification, including IFNAR1, STAT1, STAT2, and TYK2[160–168]. Moreover, an *Nsp1* mutation (ΔD500–532) frequent in viral variants is associated with even lower levels of type I IFN production[169]. It remains to be tested whether the ability of SARS-CoV-2 to resist type I IFN is also increasing in emerging variants, such as B.1, B.1.1.7 (alpha), B.1.1351 (beta), B.1.617.2 (delta), and B.1.1.529 (omicron). Current findings suggest that being able to evade type I IFN immunity is essential for viral fitness[160,170].

Viral and human fitness depend on type I IFNs

Remarkably, three targets of the virus, IFNAR1[167], IRF3[164,168], and TBK1[165], are encoded by COVID-19 susceptibility genes (Figure 1). We expect a greater convergence of viral targets and susceptibility genes to emerge with the genetic testing of viral targets *in vivo*, and the virological testing of susceptibility genes *in vitro*[158,159,171–179]. Suppression of the type I IFN response is essential for viral fitness, whereas the maintenance of type I IFN immunity is essential for human fitness. The type I IFN-blocking proteins of SARS-CoV-2 make the small amounts of type I IFN produced by infected cells in individual patients even more consequential, as attested by the catastrophic outcome of genetic or autoimmune deficiencies of type I IFN *in vivo*. Any further decrease in type I IFN levels due to the selection of new viral variants would tip the balance further in favor of the virus. Encouragingly, despite the ability of SARS-CoV-2 and its variants to evade type I IFN induction, these viral variants remain highly sensitive to type I IFN pretreatment *in vitro*[161,180]. However, the immense numbers of viral variants worldwide raise concerns about the emergence of new variants capable of impairing type I IFN immunity to an even greater extent.

Concluding remarks

IEIs of type I IFN immunity, and pre-existing auto-Abs neutralizing type I IFNs appear to be strong determinants of critical COVID-19 pneumonia in about 15-20% of patients. This is unprecedented among common infectious diseases, this proportion being much higher than the next best example, the possible explanation of tuberculosis in only 1% of European cases[19,20]. As these findings are consistent with those of *in vitro* virological studies and *in vivo* animal models[156,181–187], they may reflect a general mechanism of disease. Individuals with insufficient type I IFN in the respiratory epithelium, whatever the underlying determinants, may be unable to prevent the spread of the virus to the lungs, blood, and other organs during the first few days of infection. Inflammation may then develop when activated leukocytes, including myeloid and lymphoid cells of an innate or adaptive nature are attracted to the site of infection and attempt to resolve the pulmonary and systemic infection that became established because of the lack of control by type I IFN (Figure 2)[10,24,188]. Understandably, at such a late inflammatory stage, therapeutic type I IFN did not help hospitalized patients[189]; clinical trials of early administration in ambulatory patients are ongoing[115]. The penetrance of known IEIs of type I IFN immunity and of auto-Abs varies, with a higher penetrance for AR and XR than for AD disorders, and for auto-Abs neutralizing high concentrations of most type I IFNs relative to those neutralizing low concentrations of a single type I IFN (Table 1). Penetrance may be influenced by the size of the viral inoculum, by prior infection with other viruses that trigger type I IFN, especially in children[190], or by human determinants, such as the age-dependent decline of pDCs[163,191–194] and local respiratory type I IFN activity[36,195], or common genetic variants, including those discovered by GWAS[145–147] (Figure 3).

What underlies critical COVID-19 pneumonia in the remaining 80% of cases? It would not be surprising to discover other IEIs of type I IFN immunity, including some affecting genes encoding proteins acting upstream or downstream from type I IFNs. These findings would further clarify the pathogenesis of critical COVID-19, while revealing the corresponding redundancy of these loci against other viral infections. The considerable redundancy of type I IFN in host defense against viruses is already a major surprise. Indeed, most patients with critical COVID-19 pneumonia due to an IEI or auto-Ab production had never before been hospitalized for another severe viral illness, including patients with AR (IRF7, IFNAR1) or XR (TLR7) inborn errors of type I IFN immunity. These findings suggest that there are type I IFN-independent mechanisms of cell-intrinsic immunity providing protection against a wide range of viruses[16]. Another important question is whether adaptive immunity to the vaccine can compensate for a constitutive deficiency of type I IFN. Encouragingly, mAbs neutralizing SARS-CoV-2 protected an unvaccinated but infected child with inherited IRF9 deficiency[131]. Despite their current success, it is unclear whether vaccines will remain effective in the long term and against new viral variants[196–199]. The recent spread of the omicron variant, which is not only more contagious, but also whose protein S is structurally distant from that encoded by existing vaccines, is particularly worrisome. Even prior to the emergence of omicron, an alarming increase has been reported in the number of breakthrough cases, defined as infection in fully vaccinated individuals, including cases of hypoxemic pneumonia and even death. It is tempting to hypothesize that some IEIs or auto-Abs against type I IFN may underlie some life-threatening breakthrough cases. The search for human genetic and immunological determinants of life-threatening COVID-19 pneumonia must now encompass not only various viral variants, but also both unvaccinated and vaccinated patients.

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COVID Human Genetic Effort

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Table 1 | Major human genetic and immunological determinants of critical COVID-19 pneumonia[§]

	Risk estimate[a]	Frequency in the general population (%)	Frequency in patients with critical COVID (%)	References
Genetic risk factors				
rs73064425/ rs10490770 (3p21, intronic *LZTFL1*)	1.89 - 2.14[b]	8[c] (0.1-28)	15[d]	145–147
Known AD deficiencies (TLR3, TRIF, TBK1, IRF3)	>20[e]	<0.1	1.7	5
New AD deficiencies (UNC93B1, IRF7, IFNAR1, IFNAR2)	N.A.	0.2	1.2	5
Known AR deficiencies (IRF7, IFNAR1)	>20[e]	<0.1	0.6	5
New XR deficiency (TLR7)	34.4[f]	0.065[g]	1.3[h]	41
Immunological risk factors[i]				
anti-IFNω auto-Abs only (10 ng/mL)	2.9[j]/3.6[k]	0.2[l]	0.8	109
anti-IFNβ auto-Abs only (10 ng/mL)	4.7[j]/4.5[k]	0.3[m]	1.3	
anti-IFNα2 or anti-IFNω auto-Abs (100 pg/mL)	12.7[j]/6.9[k]	2.0[n]	13.6	
anti-IFNα2 or anti-IFNω auto-Abs (10 ng/mL)	17.5[j] /14.9[k]	0.5[l]	9.8	
anti-IFNα2 and anti-IFNω auto-Abs (10 ng/mL)	67.6[j]/29.8[k]	0.13[l]	5.6	

§. We considered as major determinants only genetic or immunological abnormalities conferring an estimated OR greater than 2. Minor risk factors have been reviewed elsewhere[12]. Note that the heritability of all common SNPs (not only the chr3p21 region) was estimated at 6.5% for severe COVID-19 in[146] and < 1% in[147]. For rare variants we provide the proportion of carriers in critical COVID-19 patients.

[a] Risk estimates are the ratio of the odds of critical COVID-19 in individuals carrying the genetic /immunological factor to those in individuals not carrying the factor. All studies compared patients with critical COVID-19 pneumonia (patients) with individuals presenting mild or asymptomatic SARS-CoV-2 infection (serving as controls), except for the GWAS of Ellinghaus et al[145], Pairo-Castineira et al[146] and the COVID-19 Host Genetics Initiative[147], which used controls from the general population.

[b] Range of odds ratios (OR) for the risk allele under an additive model accounting for ethnicity, age and sex in the GWAS by Ellinghaus et al[145], Pairo-Castineira et al[146] and the COVID-19 Host Genetics Initiative[147].

[c] The frequency is that of the risk allele observed in patients with critical COVID-19 pneumonia in the study by Pairo-Castineira et al[146].

[d] The frequency is that of the risk allele in the study by Pairo-Castineira et al[146]. The range of allele frequencies observed across nine populations of gnomAD v3 is also provided in parentheses.

[e] Based on predicted loss-of-function variants of the corresponding genes and their absence in 534 asymptomatic/paucisymptomatic infected controls. Functional tests were performed for variants from the asymptomatic/mild cases.

[f] OR adjusted for ethnicity (PCA) and age (in years) for XR TLR7 deficiency in male patients only.

[g] Cumulative MAF of biochemically deleterious *TLR7* variants in the male gnomAD general population.

[h] Proportion of critically ill male patients with XR *TLR7* deficiency.

[i] The types of type I IFN auto-Ab shown were selected both to cover the full range of ORs and to include all tested patients with critical COVID-19 pneumonia. The other data are available from Bastard et al[109].

[j] OR, adjusted for age and sex, for critical COVID-19 pneumonia relative to asymptomatic or mild infection.

[k] OR, adjusted for age and sex, for critical COVID-19 pneumonia relative to the general population.

[l] Prevalence of auto-Ab in >34,000 samples from the general population.

[m] Prevalence of auto-Ab in ~9,500 samples from the general population.

[n] Prevalence of auto-Ab in >10,000 samples from the general population.

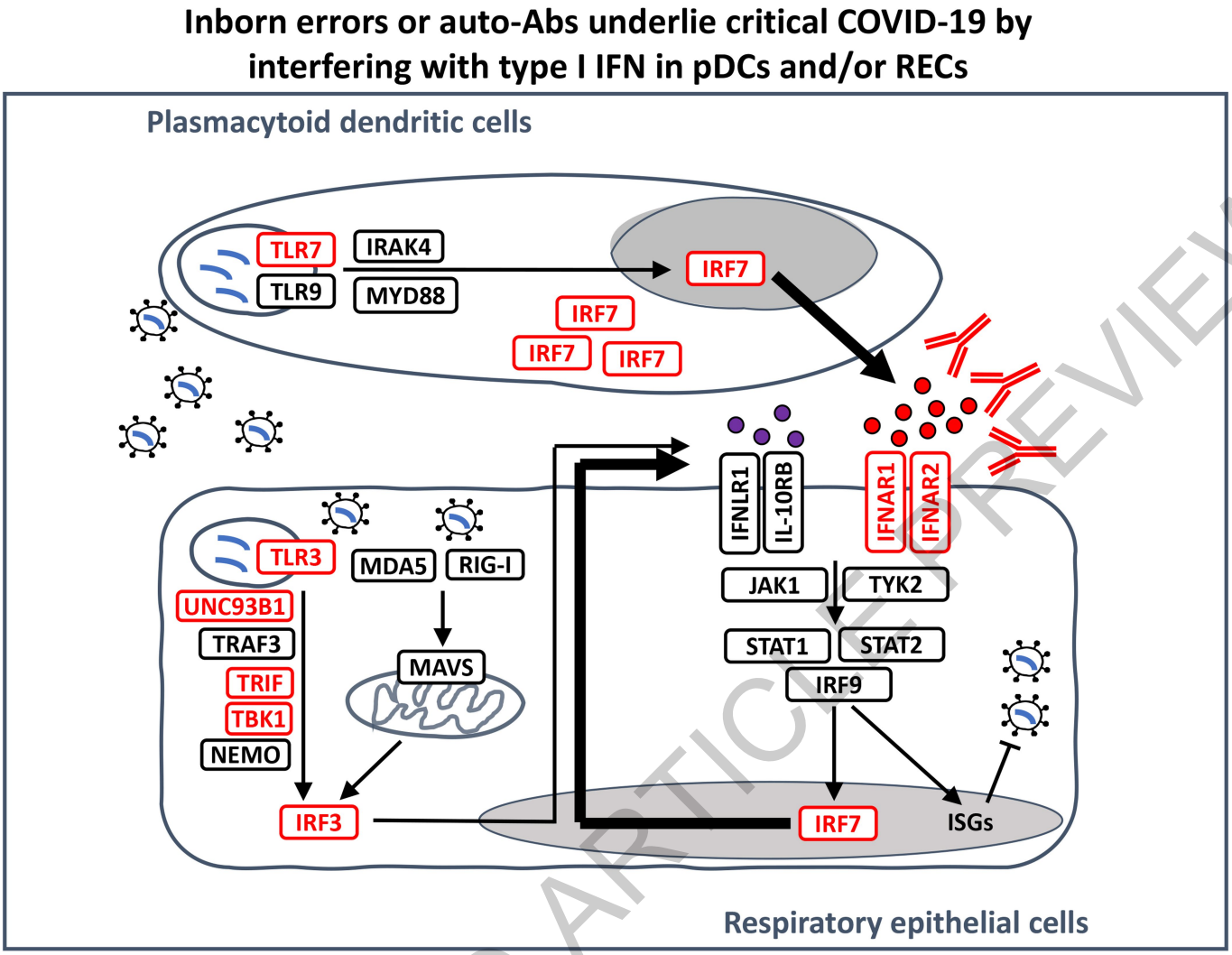

Fig. 1 | Inborn errors of type I IFN immunity and autoantibodies neutralizing type I IFNs underlie life-threatening COVID-19 pneumonia by interfering with type I IFN immunity in tissue-resident respiratory epithelial cells and blood plasmacytoid dendritic cells. There are 17 human type I IFNs, each encoded by a specific, intron-less gene: 13 subtypes of IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω, and three human type III IFNs (IFN-λ1-3). Autoantibodies to IFN-α, IFN-β, and/or IFN-ω have been identified in about 15% of patients with critical COVID-19 pneumonia. Monogenic inborn errors of TLR3- and/or TLR7-dependent type I IFN immunity have been identified in about 1-5% of patients with critical COVID-19 pneumonia (genes shown in red). SARS-CoV-2 infection can induce type I IFN production in a TLR3-dependent manner in tissue-resident respiratory epithelial cells (RECs, which express TLR3 but not TLR7) and in a TLR7-dependent manner in circulating plasmacytoid dendritic cells (pDCs, which express TLR7 but not TLR3)[200]. IRF7 is constitutively expressed in pDCs, at higher levels than in other cell types, whereas it is mostly induced by viral infection in RECs[200]. IRF7 activation is required to produce type I IFNs other than IFN-β[33]. IFN: interferon; Auto-Ab: autoantibody, ISGs: interferon-stimulated genes.

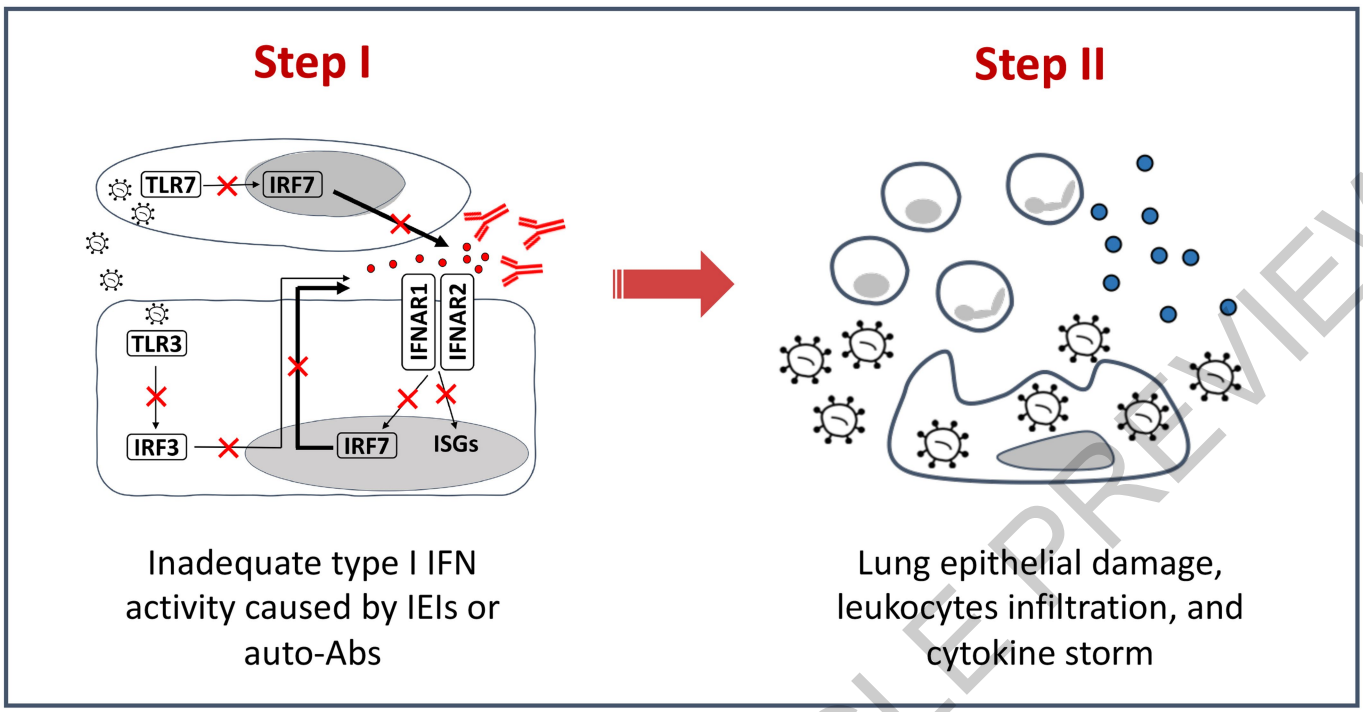

Fig. 2 | Inborn errors of type I IFN immunity and autoantibodies neutralizing type I IFNs underlie life-threatening COVID-19 pneumonia by facilitating the spread of the virus during the first few days of infection, triggering secondary leukocytic inflammation. In a two-step model of pathogenesis of critical COVID-19[12], inadequate type I IFN immunity during the first few hours and days of infection results in the spread of the virus to the lungs, blood, and beyond. This results, one to two weeks later, in pulmonary and systemic hyperinflammation, largely due to the recruitment and activation of leukocytes, which produce excessive amounts of cytokines in a last-ditch attempt to eradicate the virus that should have been eradicated by type I IFN but was not. The two-step model suggests that early administration of type I IFN at the onset of SARS-CoV-2 infection, in ambulatory patients, or even before infection in exposed individuals at risk of severe disease, may halt disease progression in patients without auto-Abs to the corresponding type I IFN and without IEIs downstream from type I IFN receptors. IFN: interferon; IEI: inborn errors of immunity; Auto-Ab: autoantibody, ISGs: interferon-stimulated genes.

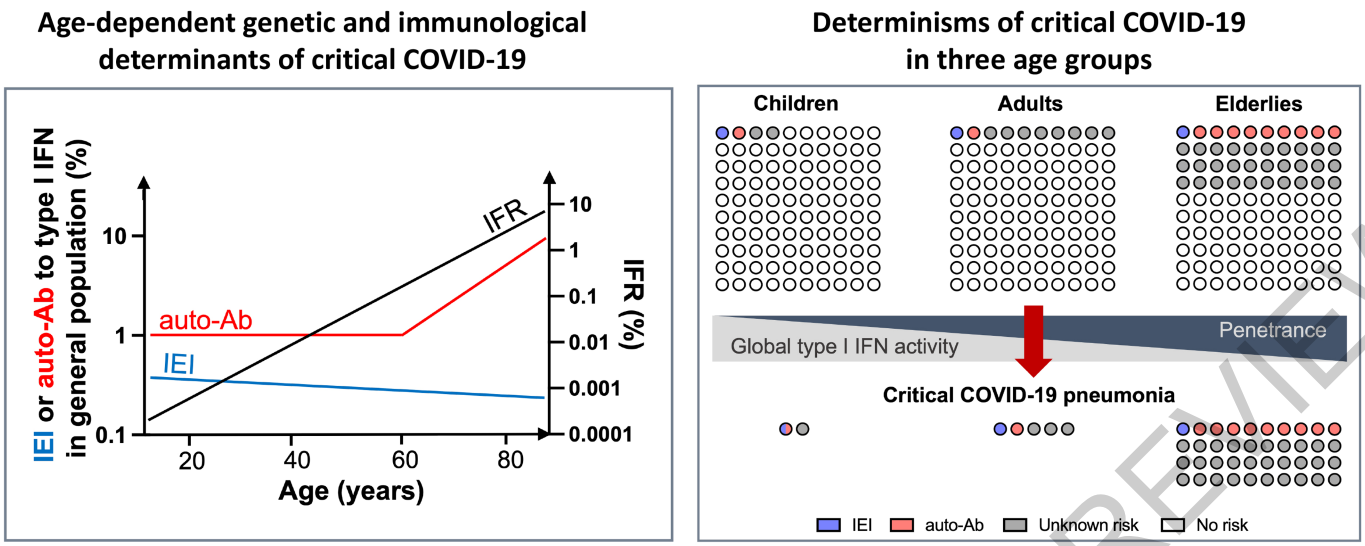

Fig. 3 | Inborn errors of type I IFN immunity and autoantibodies neutralizing type I IFNs underlie life-threatening COVID-19 pneumonia by aggravating the natural age-dependent decline of type I IFN immunity in the mucosae and blood. Inborn errors of type I IFN immunity conferring predisposition to critical COVID-19 pneumonia are represented in slightly declining proportion across age groups in the general population, as they may underlie critical influenza and related life-threatening viral illnesses. In contrast the frequency of auto-Abs against type I IFN increases exponentially after the age of 65 years (*y* axis on the left), attesting to a breakdown of tolerance in the elderly population. Global type I IFN immunity in the respiratory tract mucosae (RECs) and in the blood (pDCs) is shown to decline with age, under the influence of aging and environmental triggers[190,191]. This decline in global type I IFN immunity over time may increase the risk of life-threatening COVID-19 (referred to as penetrance, for both IEI and autoantibodies) associated with genetic and immunological etiologies in elderly patients. All three risk factors – IEIs, auto-Abs, and tonic levels of type I IFNs – may contribute to critical COVID-19 pneumonia (right panel). IEIs and auto-Abs appear to affect different patients, while the gradual decrease in tonic levels of type I IFNs can aggravate the consequences of both IEIs and auto-Ab. Overall, the cohort of patients with life-threatening COVID-19 is enriched with IEI in young patients and with auto-Abs in elderly patients. IEI: inborn errors of immunity; IFR: infection-fatality ratio; auto-Ab: autoantibody.