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Human autoantibodies neutralizing type I IFNs: From 1981 to 2023

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Summary

Human autoantibodies (auto-Abs) neutralizing type I IFNs were first discovered in a woman with disseminated shingles and were described by Ion Gresser from 1981 to 1984. They have since been found in patients with diverse conditions and are even used as a diagnostic criterion in patients with autoimmune polyendocrinopathy syndrome type 1 (APS-1). However, their apparent lack of association with viral diseases, including shingles, led to wide acceptance of the conclusion that they had no pathological consequences. This perception began to change in 2020, when they were found to underlie about 15% of cases of critical COVID-19 pneumonia. They have since been shown to underlie other severe viral diseases, including 5%, 20%, and 40% of cases of critical influenza pneumonia, critical MERS pneumonia, and West Nile virus encephalitis, respectively. They also seem to be associated with shingles in various settings. These auto-Abs are present in all age groups of the general population, but their frequency increases with age to reach at least 5% in the elderly. We estimate that at least 100 million people worldwide carry auto-Abs neutralizing type I IFNs. Here, we briefly review the history of the study of these auto-Abs, focusing particularly on their known causes and consequences.

This article is part of a series of reviews covering Inborn Errors in Immunity appearing in Volume 322 of *Immunological Reviews*.

Paul Bastard, Adrian Gervais, Tom Le Voyer, Quentin Philippot and Aurélie Cobat have equal contributions.

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1 | INTRODUCTION

Not all individuals exposed to any given pathogen become infected and the impact of infection is highly variable, from silent infection to lethal disease. Many historically lethal infections can now be prevented or cured with modern medicine. Nevertheless, the outcome of any infection in any given population remains highly diverse, due to differences in the genetic and immunological status of infected humans, with life-threatening infection attesting, by definition, to an inherited or acquired immunodeficiency.¹ Monogenic inborn errors of immunity (IEIs) have provided particular insight in this respect, as they can underlie severe infectious diseases in otherwise healthy individuals normally resistant to other infections.^{2,3} For example, IEIs affecting the production or response pathways for any of five different cytokines disrupt immunity to specific pathogens.^{4–6} Patients with inborn errors of interferon (IFN)- γ (type II IFN) immunity are vulnerable to weakly virulent mycobacteria (Mendelian susceptibility to mycobacterial disease, MSMD) and to the more virulent *Mycobacterium tuberculosis*.⁷ Patients with inborn errors of IL-6R are at risk of staphylococcal disease.^{8,9} Patients with inborn errors of IL-17A/IL-17F (IL-17A/F) suffer from chronic mucocutaneous candidiasis (CMC).¹⁰ To our knowledge, Inborn errors of GM-CSF have not yet been shown to underlie specific infections.^{11–13} Finally, inborn errors of IFN- α/β (type I IFN) immunity underlie several severe viral diseases, including herpes simplex virus 1 (HSV-1) encephalitis (HSE),^{14,15} critical influenza A virus pneumonia,¹⁶ critical COVID-19 pneumonia,^{17,18} and adverse reactions to live attenuated measles^{19–21} or yellow fever virus vaccines.^{19,22}

Some patients with autoimmune phenocopies of these genetic deficiencies display similar infectious phenotypes, due to autoantibodies (auto-Abs) neutralizing specific cytokines.^{23,24} The infectious

phenotype of these patients is indistinguishable from that seen in patients carrying an inborn error of the corresponding cytokine or its receptors, although other differences may be observed.^{23,25,26} Autoimmune phenocopies of five cytokines have been described.^{6,23,24} Neutralizing anti-IFN- γ autoantibodies (nAIGA) confer a predisposition to environmental mycobacterial disease and related intramacrophagic infections.^{23,26} Since 2004, hundreds of patients with nAIGAs have been described.^{26–30} Most of these patients were adults originating from East Asia^{23,26,31,32} and carrying either of the two specific HLA class II DRB1 alleles (15:02 and 16:02).^{33,34} Since 2008, patients with neutralizing auto-Abs against IL-6 have been reported.^{35–37} These patients suffer from recurrent subcutaneous staphylococcal abscesses or other severe pyogenic infections, and their serum C-reactive protein (CRP) levels remain low during infection. In 2010, auto-Abs neutralizing IL-17A/F cytokines were found in patients with autoimmune polyendocrinopathy syndrome type I (APS-1), whose CMC had long remained a mystery among their various autoimmune manifestations.^{38,39} Since 1999, high titers of auto-Abs neutralizing GM-CSF have been reported in patients with idiopathic pulmonary alveolar proteinosis (PAP),^{13,40} and in 2013, these same auto-Abs were discovered for the first time in patients with cerebral nocardiosis⁴¹ or cryptococcosis.^{31,42–52} Patients treated with biologics inhibiting some of these pathways also suffer from similar infections, as reported for patients treated with a monoclonal antibody targeting the type I IFN receptor, who suffer from viral infections,⁵³ and patients treated with anti-IL17A/F monoclonal antibodies, who suffer from candidiasis.^{54,55} By 2019, just before the COVID-19 pandemic, it was already widely known that auto-Abs neutralizing specific cytokines can cause mycobacterial disease (IFN- γ , type II IFN), staphylococcal disease (IL-6), invasive nocardiosis or cryptococcosis (GM-CSF), and mucocutaneous candidiasis (IL-17A/F).

Auto-Abs neutralizing cytokines are present before infection and are causal for severe infectious disease. Conversely, other types of auto-Abs have been shown or are thought to be triggered by infection; the pathogenic contribution of such antibodies remains unclear. An interesting example is provided by Guillain-Barré syndrome (GBS) in which, following a benign infection, the molecular mimicry between a common pathogen and peripheral nerves can lead to the development of anti-ganglioside auto-Abs leading to acute flaccid paralysis.^{56,57} The infection itself is usually benign, with self-limited gastrointestinal manifestations, but it leads to the production of specific antibodies because, for example, of particular ganglioside-like structures in the wall of *Campylobacter jejuni* bacteria which may, in some cases, mimic "self", leading to the production of anti-ganglioside auto-Abs and the onset of this severe neurological condition several weeks after infection. To our knowledge, no other causal link has ever been made between an infection and the onset of an autoimmune disease (i.e., auto-Abs directly triggered by the infection leading to a post-infection condition). It remains unclear why only a few individuals infected with *C.jejuni* (or other pathogens) develop GBS. Nevertheless, infections, and viral infections in particular, have frequently been identified as potential triggers of relatively common autoimmune conditions, such as hemolytic anemia, systemic lupus erythematosus (SLE), and multiple sclerosis.⁵⁸ At the start of the COVID-19 pandemic, five examples of auto-Abs preexisting infection and causing disease were known, together with one example of auto-Abs triggered by infection and causing post-infectious manifestations.

2 | AUTO-ABS NEUTRALIZING TYPE I IFNS, FROM 1981 TO 2019

Type I interferons (IFNs) were first described in 1957; they are present in all jawed vertebrate species and are potent antiviral molecules effective against most viruses.^{59,60} The 16 types of human type I IFNs (12 IFN- α subtypes encoded by 13 loci, IFN- β , IFN- ϵ , IFN- κ , and IFN- ω) are closely related phylogenetically and biochemically, all binding to the same heterodimeric receptor consisting of IFNAR1 and IFNAR2 chains, but their individual functions are not fully understood.^{61,62} The 12 subtypes of IFN- α and IFN- ω are low-affinity, long-lived, systemic IFNs mostly produced by leukocytes, including plasmacytoid dendritic cells (pDCs) in particular.^{63,64} By contrast, IFN- β is a high-affinity, short-lived, autocrine IFN produced by most, if not all cell types, both constitutively and upon stimulation; it confers protection against viruses directly and by inducing the other type I IFNs.^{63,65} IFN- ϵ and IFN- κ are expressed in the female reproductive tract and the skin, respectively.^{66,67} IFN- ϵ was recently shown to restrict ovarian cancer.⁶⁸ Studies of human monogenic type I interferonopathies have revealed that excessive type I IFN activity in vivo is pathogenic, particularly in the skin, respiratory tract, and central nervous system (CNS).⁶⁹ By contrast, some severe viral illnesses, including adverse reactions to live attenuated viruses (against measles or yellow fever), severe influenza pneumonia, and

herpes simplex virus 1 (HSV-1) encephalitis (HSE), can be caused by inborn errors impairing the production of, or the response to type I IFNs.^{15,18-21,70-76} Moreover, in 2020, some patients with hypoxemic COVID-19 pneumonia were found to harbor inborn errors affecting the production of, or the response to type I IFNs.^{17,18} This raised questions as to whether auto-Abs neutralizing type I IFNs present before infection could mimic inborn errors of type I IFN immunity and underlie critical COVID-19 pneumonia.

This raises a paradox. Auto-Abs neutralizing type I IFNs causal for a severe viral disease were initially described in a single patient between 1981 and 1984, yet were long thought to be clinically silent, after their discovery in many patients with no apparent susceptibility to severe viral disease. Indeed, auto-Abs neutralizing type I IFNs were described in patients treated with IFN- α or IFN- β , for hepatitis C, for example, from 1981 onwards.^{77,78} Importantly, Ion Gresser described such auto-Abs in an elderly woman with severe disseminated VZV infection between 1981 and 1984.^{79,80} Despite this description, it took more than 30 years for these auto-Abs to be recognized as responsible for viral diseases. They were detected in patients with SLE in 1982^{81,82} and were subsequently shown to decrease disease activity by attenuating the type I IFN signature, but no association with severe viral diseases was identified at this point.^{83,84} In 2003, auto-Abs against type I IFNs were described in patients with thymoma,⁸⁵ and in patients with myasthenia gravis with or without thymoma.^{86,87} In 2006, they were shown to be a diagnostic marker (i.e., present in most, if not all cases from infancy onward) for APS-1, which is caused by allelic variants of *AIRE*.⁸⁸⁻⁹⁰ Nine years later, in 2015, they were described in patients with hypomorphic variants of *RAG1* or *RAG2* and combined immunodeficiency.⁹¹ Interestingly, these auto-Abs appeared to be associated with an increase in the risk of severe viral diseases, such as severe varicella, vaccine-associated varicella, and viral encephalitis after anti-yellow fever vaccination.²² However, the T- and B-cell deficits of the patients were highly variable, which confounded the interpretation of this association.⁹¹ Finally, in 2018, these auto-Abs were found in men with deleterious variants of *FOXP3* and immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX).⁹² Thus, in 2019, the impact of auto-Abs neutralizing type I IFNs on the pathogenesis of viral disease had not yet been established.

3 | AUTO-ABS NEUTRALIZING TYPE I IFNS, FROM 2020 ONWARDS

It was not until the COVID-19 pandemic that the pathogenicity of auto-Abs neutralizing type I IFNs was finally demonstrated and accepted. In a large international cohort of adult patients with life-threatening COVID-19 pneumonia (COVID Human Genetic Effort, www.covidhge.com), ~10 to 15% of cases were found to be due to preexisting auto-Abs neutralizing type I IFNs and the prevalence of these auto-Abs was as high as ~20% in the patients who died.^{3,93-96} Among critically ill COVID-19 patients carrying auto-Abs neutralizing type I IFNs, the proportion of male patients was higher than that

of female patients and the prevalence of these antibodies was found to be higher in elderly patients.^{93,94} More than 75% of the APS-1 patients from known cohorts, all of whom were known to carry auto-Abs neutralizing type I IFNs before infection with SARS-CoV-2, were hospitalized for COVID-19 pneumonia.^{97,98} In all cases tested, these auto-Abs blocked the protective effect of type I IFNs against SARS-CoV-2 in vitro.^{93,99} These findings were widely replicated in dozens of independent cohorts worldwide.^{83,97,100–134} The auto-Abs typically neutralize IFN- α , IFN- ω , or IFN- β . Interestingly, auto-Abs neutralizing IFN- α 2 usually neutralize all the other 11 IFN- α subtypes, perhaps leading to a higher risk of severe viral disease.^{93,94} However, even auto-Abs neutralizing only IFN- ω underlie a higher risk of disease. Tests were not performed for auto-Abs neutralizing IFN- ϵ and IFN- κ , as their activity levels, which are 1000-fold lower than those of the other type I IFNs, made this difficult, and their expression patterns rendered them less relevant to COVID-19 pneumonia. Neutralizing auto-Abs against IFN- α , IFN- β , or IFN- ω were found to confer a higher risk of life-threatening disease, particularly if they neutralized high concentrations of both IFN- α 2 and IFN- ω ; patients with such antibodies had a >100-fold higher risk of life-threatening disease than individuals without auto-Abs.^{94,95,99} Strikingly, these auto-Abs were also described in ~24% of a cohort of “breakthrough” hypoxemic COVID-19 pneumonia cases tested, despite having received two doses of mRNA vaccine and mounted an antibody response capable of neutralizing SARS-CoV-2 in vitro.¹³⁵ Finally, we studied 183 unvaccinated children hospitalized for COVID-19 pneumonia. Nineteen (10.4%) harbored auto-Abs neutralizing type I IFNs, and the odds ratios (ORs) for life-threatening COVID-19 pneumonia were higher in children and adults with auto-Abs neutralizing IFN- α 2.⁹⁹

We then assessed the prevalence of auto-Abs neutralizing type I IFNs in the general uninfected population. Only four of the 16 human type I IFNs are glycosylated (IFN- α 2a/b, IFN- α 14, IFN- ω , IFN- β). Auto-Abs against glycosylated IFN- α 2 and IFN- ω have not been investigated in the general population, but a high rate of concordance was found in patients between auto-Abs neutralizing the glycosylated and unglycosylated forms.^{99,136} The prevalence of auto-Abs in the blood neutralizing 10ng/mL glycosylated IFN- β , and 10ng/mL and 100pg/mL unglycosylated IFN- α 2 and IFN- ω was assessed in large samples, including 2267 children (from 0 to 18 years old),⁹⁹ and 39,198 adults (from 18 to 100 years old),^{94,95,109} sampled before the COVID-19 pandemic. Auto-Abs neutralizing IFN- α 2, regardless of the presence or absence of auto-Abs neutralizing IFN- ω , are rare in children (0.05% for auto-Abs with neutralizing activity against 10ng/mL and 0.2% for auto-Abs with neutralizing activity against 100pg/mL) and in adults under 65 years of age (0.07% for auto-Abs with neutralizing activity at 10ng/mL and 0.3% for auto-Abs with neutralizing activity at 100pg/mL). Strikingly, the prevalence of these antibodies increases strongly with age, from 1% (for neutralizing activity against 10ng/mL) and 2.6% (for neutralizing activity against 100pg/mL) in carriers over the age of 65 years, reaching 2.4% and 4.7%, respectively, in carriers over the age of 80 years. Auto-Abs neutralizing IFN- ω , regardless of the presence or absence

of auto-Abs neutralizing IFN- α 2, are more frequent than those neutralizing IFN- α 2 or IFN- β in children (0.3% for auto-Abs with neutralizing activity against 10ng/mL and up to 2% for auto-Abs with neutralizing activity against 100pg/mL) and in adults under the age of 65 years (0.1% and 0.85%, respectively). The prevalence of auto-Abs neutralizing IFN- ω also increases after the age of 65 years (0.8% for auto-Abs with neutralizing activity against 10ng/mL and 2.2% for auto-Abs with neutralizing activity against 100pg/mL), reaching 1.9% and 3.82%, respectively, after the age of 80 years, although this increase is less pronounced than that for IFN- α 2. Auto-Abs capable of neutralizing glycosylated IFN- β at a concentration of 10ng/mL are present in 0.04% of children, 0.3% of adults below 65 years of age, and 0.18% of the elderly (over 65 years of age). Auto-Abs neutralizing at least one type I IFN are found in 2.1% of children below the age of 18 years, 1.6% of individuals below the age of 65 years, and 4.8% of the elderly. The prevalence of auto-Abs neutralizing IFN- α 2 increases eight-fold after the age of 65 years, especially in men, in whom the increase was as great as 10-fold, whereas the prevalence of auto-Abs neutralizing IFN- ω increases only 2.5-fold.⁹⁹

4 | TISSUE DISTRIBUTION OF AUTO-ABS NEUTRALIZING TYPE I IFNS

The nasopharyngeal mucosa is the port of entry of SARS-CoV-2. The impact of auto-Abs against type I IFNs on the induction of type I or type III IFN-dependent IFN-stimulated genes (ISGs) in the nasopharyngeal mucosa was studied in unvaccinated patients with life-threatening COVID-19 pneumonia.¹³⁷ Interestingly, 63% of patients with auto-Abs against type I IFNs displayed impaired ISG induction in the nasopharyngeal mucosa on admission to the ICU. Moreover, half the patients with serum auto-Abs neutralizing type I IFNs had the same auto-Abs in their nasopharyngeal mucosa, demonstrating that auto-Abs against type I IFNs can reach the upper respiratory tract. This study suggested that auto-Abs against type I IFNs compromise early antiviral defenses against SARS-CoV-2 in the upper respiratory tract, as in the tracheal aspirates,¹³⁸ and in blood, thereby contributing to the spread of the virus to other tissues.^{18,139,140} For the lower respiratory tract, we searched for auto-Abs against type I IFNs in the bronchoalveolar lavage (BAL) of a cohort of unvaccinated patients with life-threatening COVID-19 pneumonia. We found auto-Abs neutralizing type I IFNs in the BAL of 54 of the 415 patients (13%) tested.¹³⁰ Paired plasma samples were available for seven patients with auto-Abs in plasma. All but one of these patients had detectable auto-Abs in both the serum and BAL. Auto-Abs neutralizing type I IFNs are, therefore, present in the alveolar space of over 10% of patients with life-threatening COVID-19 pneumonia, providing further evidence for their contribution to pathogenesis.

These findings suggest that the IgG auto-Abs against type I IFNs circulating in the plasma can reach the alveolar space. In our study, the epithelial lining fluid was estimated to be diluted ~100-fold in the BAL samples tested. Auto-Abs neutralizing lower concentrations of type I IFNs may, therefore, have remained undetected. We know

that these auto-Abs are present in the plasma before SARS-CoV-2 infection.^{94,97} Moreover IgG antibodies are present in the epithelial lining fluid of healthy individuals.¹⁴¹ Auto-Abs neutralizing type I IFNs are, thus, probably present in the alveolar space before SARS-CoV-2 infection. Like auto-Abs neutralizing type I IFNs in the nasopharyngeal mucosa, auto-Abs neutralizing type I IFNs in the BAL may contribute to the spread of the virus to and within the lower respiratory tract.¹³⁷ In the nasopharyngeal mucosa, these antibodies are associated with a decrease in type I/III IFN-dependent ISG induction.¹³⁷ The detection of neutralizing auto-Abs against type I IFNs in patient plasma is associated with lower levels of interferon-stimulated gene (ISG) expression in the blood,¹⁰⁹ and with an absence of detectable type I IFNs in the blood of patients with auto-Abs neutralizing the highest doses of type I IFNs.⁹³ Overall, auto-Abs neutralizing type I IFNs in the blood and respiratory tract impair antiviral type I IFN immunity and contribute to life-threatening COVID-19 pneumonia.^{130,137} It would now be interesting to study the presence of auto-Abs against type I IFNs in other tissues.

5 | GENETIC CAUSES OF AUTO-ABS AGAINST TYPE I IFNS

Evidence that auto-Abs neutralizing type I IFNs have a genetic basis was provided by studies of IEIs affecting central T-cell tolerance (Figure 1). The first inborn error reported to underlie the development of these antibodies was APS-1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). This syndrome was initially described clinically in 1929 in a patient with the classical APS-1 triad of Addison's disease, hypoparathyroidism, and CMC.¹⁴² APS-1 is a rare condition with a prevalence of around 1/200,000, but with a higher frequency in Sardinia (1 in 14,400) and Finland (1 in 25,000) due to founder effects.¹⁴³ Patients with APS-1 carry germline biallelic deleterious variants of AIRE, which encodes a protein almost exclusively expressed in medullary thymic epithelial cells (mTECs).¹⁴⁴ AIRE acts as a critical regulator of central T-cell tolerance, promoting the expression of thousands of tissue-specific self-antigens (TSAs) to ensure the deletion of the corresponding thymocytes.¹⁴⁵ APS-1 patients, who have defective AIRE function, develop multiple organ-specific autoimmune T-cell diseases frequently affecting endocrine/exocrine glands or, more rarely, other organs.¹⁴⁶ They also present a wide range of tissue-specific auto-Abs, and frequently harbor auto-Abs neutralizing IL-17A and/or IL-17F, which underlie their CMC.^{10,38,90,147} Studies performed since 2006 have shown that almost all APS-1 patients also produce auto-Abs against type I IFNs from early childhood onward.^{38,39,89,90} The detection of these auto-Abs has even been developed as a diagnostic test for APS-1.^{148,149} About a third of patients with autosomal dominant (AD) APS-1, caused by dominant-negative AIRE variants and associated with milder autoimmunity, also develop auto-Abs against IFN- α and/or IFN- ω .¹⁵⁰⁻¹⁵⁵ Patients with thymoma, a thymic epithelial tumor,¹⁵⁶ frequently develop T-cell or Ab-mediated autoimmune disease (including late-onset myasthenia gravis,¹⁵⁷ and

tissue-specific auto-Abs of the APS-1 spectrum¹⁵⁸⁻¹⁶⁰). They harbor auto-Abs against IL-17A/F, which are associated with the occurrence of the CMC,^{38,158,159,161} and about ~70% of patients have auto-Abs against type I IFNs,^{87,158,162} leading to a particularly high fatality rate for COVID-19, especially in patients with Good syndrome (the association of thymoma and immunodeficiency).¹⁶³⁻¹⁷³ Interestingly, neoplastic mTECs do not express AIRE,^{174,175} suggesting that the breakdown of T-cell tolerance is a consequence of impaired central tolerance linked to impaired AIRE expression in the neoplastic tissue.

The alternative (or non-canonical) NF- κ B pathway is dependent on the NF- κ B-inducing kinase (NIK), IKK α , NF- κ B2, and RelB through the formation of the p52/RelB heterodimer.¹⁷⁶ Patients with inborn errors of the alternative NF- κ B pathway carrying biallelic loss-of-function (LOF) variants of NIK or RelB or monoallelic p52^{LOF}/IkB δ ^{GOF} variants of NF- κ B2 were also recently shown to carry neutralizing auto-Abs against type I IFNs in more than 80% of cases.¹⁷⁷ The thymuses of patients with AR RelB deficiency or heterozygous for a p52^{LOF}/IkB δ ^{GOF} variant are abnormally structured and present impaired AIRE expression in mTECs.¹⁷⁷ The presence of auto-Abs neutralizing type I IFNs in patients with inborn errors of the alternative NF- κ B pathway persisted even after hematopoietic stem cell transplantation (HSCT), further suggesting that their development was caused by the impaired development of thymic stromal cells. Inborn errors of the alternative NF- κ B pathway define the second group of causal inborn errors in terms of the prevalence of auto-Abs against type I IFNs in the corresponding patients. Together with APS-1, these disorders delineate a general mechanism underlying the development auto-Abs against type I IFNs, with an mTEC-intrinsic deficiency of AIRE disrupting thymic T-cell tolerance to type I IFNs. Surprisingly, women with X-linked dominant ectodermal dysplasia caused by loss-of function germline variants of the *IKBKG/NEMO* gene⁶³⁻⁶⁵ – thought normally to cause only abnormalities in ectoderm-derived tissues, such the skin, eyes, teeth, hair, breasts, nails and CNS – were found to have auto-Abs neutralizing type I IFNs.^{93,178} Indeed, we analyzed 119 women with IP from 89 kindreds in 10 countries and found that 44 of these women (37%) had auto-Abs neutralizing IFN- α and/or IFN- ω , a frequency 45 times higher than that in aged-matched women from the general population. Imaging revealed that the thymus was small and abnormally structured in vivo in women with IP. Thus, at least a third of women with IP have thymic abnormalities, including a hypotrophic thymus and have an mTEC development defect, underlying the production of auto-Abs neutralizing type I IFNs.

Another group of inborn errors of type I IFN immunity affect T-cell intrinsic tolerance. Hypomorphic biallelic RAG1 or RAG2 variants restrict TCR diversity and cause Omenn syndrome (OS) or combined immune deficiency (CID) of variable severity.¹⁷⁹ These variants allow a sufficient T-cell development and recombination activity to support clonotypic T-cell expansions and organ-related autoimmunity.¹⁷⁹ About 60% of patients with biallelic hypomorphic RAG variants develop auto-Abs against type I IFNs.⁹¹ In these patient, the thymus does not express AIRE due to insufficient thymic cross-talk between developing T cells and immature mTECs to ensure correct

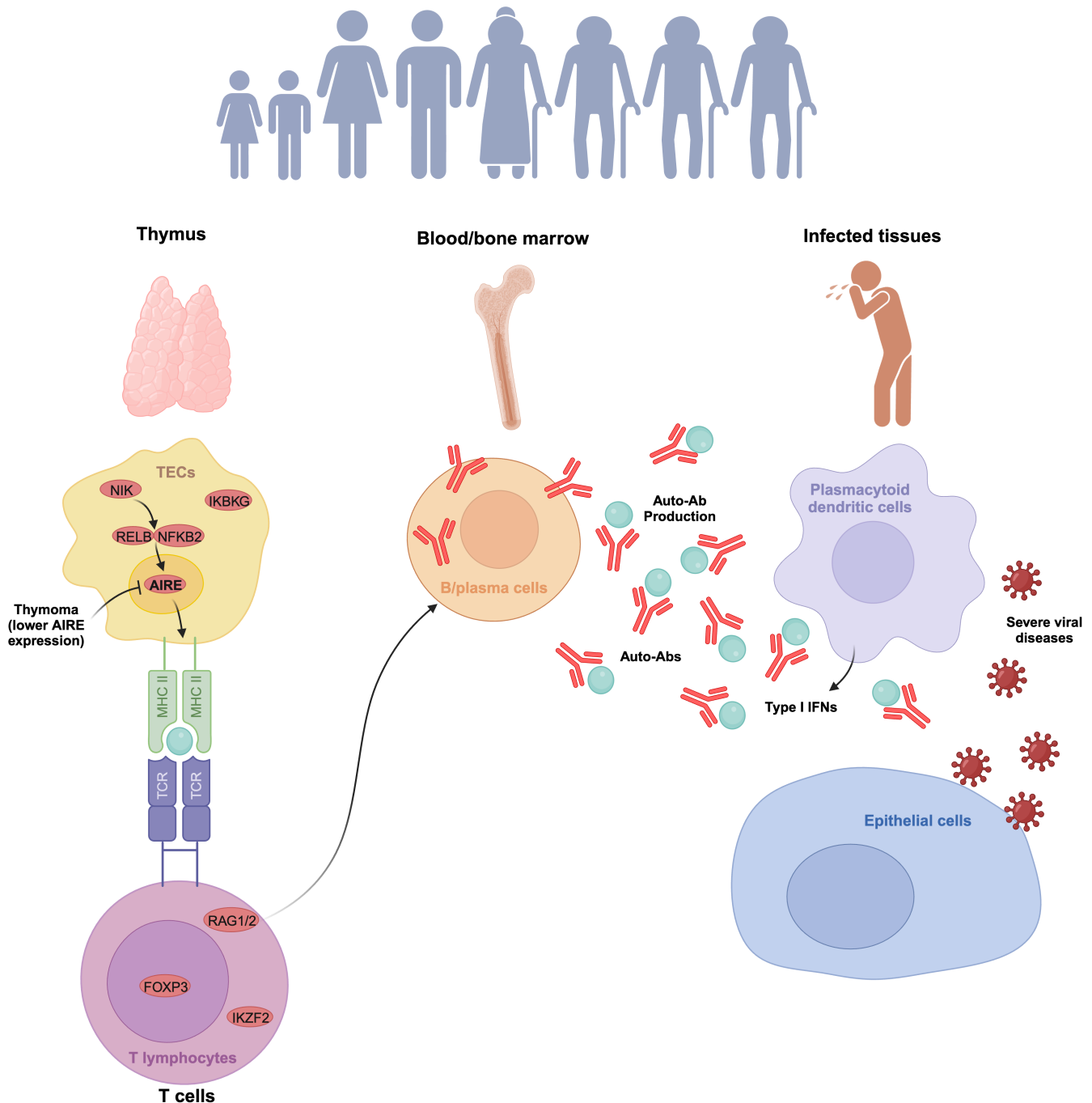


FIGURE 1 Causes and consequences of auto-Abs neutralizing type I IFNs. Thymic defects of epithelial cells (e.g., APS-1) or thymocytes (e.g., IPEX) can lead to the production of auto-Abs against type I IFNs by type I IFN-specific B cells and plasmacytes. These defects can be inherited (e.g., APS-1, IPEX) or acquired (e.g., thymoma). Upon viral infection, when type I IFNs are produced by infected cells in the tissues as well as by newly recruited plasmacytoid dendritic cells, their activity is blocked by neutralizing auto-Abs, leading to higher viral replication and severe disease. Ab, antibody; AIRE, Autoimmune regulator; APS-1, autoimmune polyendocrine syndrome type 1. FOXP3, forkhead box P3. IKAROS Family Zinc Finger 2. IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked. RELB Proto-Oncogene, NF- κ B Subunit; IFNs, interferons; IKBKG, inhibitor of nuclear factor kappa-B kinase subunit gamma; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; NIK, NF-kappa-B-inducing kinase; RAG, Recombination-activating gene; TEC, thymic epithelial cells. Created with [BioRender.com](https://www.biorender.com).

central tolerance.¹⁸⁰⁻¹⁸³ Allogeneic HSCT remains the only curative option for patients with RAG deficiency.¹⁸⁴ However, the resulting correction of the T- and B-cell compartments may be insufficient to overcome the established stromal defect, and these patients may

be at risk of developing autoimmunity or viral diseases after transplantation, like patients with inborn errors of the alternative NF- κ B pathway. The spectrum of auto-Abs in patients with hypomorphic RAG variants is broader than that in patients with inborn errors of

the alternative NF- κ B pathway,⁹¹ as patients with RAG1/2 deficiency may develop APS-1-related auto-Abs such as IL-17A/F and IL-22, underlying CMC in APS-1. Finally, auto-Abs against type I IFNs have been reported in patients with inborn errors of regulatory T cells (Tregs). Patients with immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome caused by deleterious hemizygous variants of *FOXP3* develop early-onset multiorgan autoimmunity. A third of these patients over the age of 1 year develop auto-Abs that partially neutralize IFN- α 2.⁹² They do not appear to develop auto-Abs against IFN- ω , IL17A/F or IL-12/23.⁹² It is unclear whether these auto-Abs develop because of impaired peripheral T-cell tolerance or because of the impact of *FOXP3* deficiency on the thymus, as in patients with RAG mutations. Auto-Abs against IFN- α and IFN- ω were also reported in a patient with a monoallelic truncating variant of *IKZF2*, which encodes Helios, a protein expressed primarily in Tregs.¹⁸⁵ Thus, several germline genetic defects affecting mTECs or T cells have been associated with the occurrence of auto-Abs against type I IFNs.

6 | CONSEQUENCES OF AUTO-ABS AGAINST TYPE I IFNS: VIRAL INFECTIONS OTHER THAN COVID-19

Since 2003, inborn errors of type I IFNs have been shown to underlie a surprisingly narrow range of severe viral diseases.^{18–20,70,72–75,93,186,187} Unsurprisingly, autoimmune phenocopies of these inborn errors have also been shown to underlie these severe viral diseases. Auto-Abs neutralizing type I IFNs underlie severe types of viral pneumonia other than that associated with COVID-19. Auto-Abs neutralizing IFN- α 2 alone or with IFN- ω were found to account for ~5% of cases of life-threatening influenza pneumonia in patients <70 years old, and to increase substantially the relative risk of developing severe disease¹⁴⁰ (Table 1). The patients' auto-Abs increased influenza A virus replication in both A549 cells and reconstituted human airway epithelia. Moreover, these auto-Abs were found in ~24% of patients hospitalized for Middle East respiratory syndrome (MERS) from a cohort of 62 patients in Saudi Arabia.¹⁸⁸ Over 90% of the auto-Ab-positive patients hospitalized in the ICU in this study were critically ill with MERS.¹⁸⁸ Auto-Abs were present before the infection in all cases tested. Overall, auto-Abs neutralizing type I IFNs account for a significant proportion of severe viral infections of the lungs. The underlying mechanism probably involves neutralization of the IFNs produced by pDCs, and of those produced by respiratory epithelial cells. Inherited IRF7 deficiency provides some insight in this respect, as patients with this deficiency are selectively prone to respiratory viral infections. IRF7 deficiency abolishes the induction of type I IFNs other than IFN- β .

Auto-Abs against type I IFNs were generally thought to be silent before the COVID-19 pandemic, but they were first described in a 77-year-old woman with disseminated shingles and no history of severe viral disease.⁷⁹ Interestingly, patients with IFNAR1/2 deficiency have been shown to suffer from herpes simplex encephalitis,¹⁵

adverse reactions to live attenuated VZV vaccination,¹⁸⁹ but these patients are not particularly susceptible to CMV or VZV infection, VZV reactivation or cutaneous HSV1/2 infections, perhaps because they are affected by other viral infections first. Recently, in a cohort of critically ill COVID-19 patients, auto-Abs neutralizing type I IFNs were identified as a risk factor for severe HSV-1/2 infections, a feature reminiscent of the first case reported in the 1980s.¹²¹ These auto-Abs appeared to be associated with a greater risk of CMV infection or infection with both HSV1/2 and CMV, whereas the association was not significant for HSV1/2 alone (Table 1). These findings are also reminiscent of those for patients with hypomorphic mutations of *RAG1* or *RAG2*.⁹¹ Overall, these findings indicate that anti-IFN autoantibodies may contribute to viral disease due to HSV1/2 or CMV. APS-1 patients are susceptible to VZV disease (pneumonia),¹⁹⁰ and/or VZV reactivation.¹⁹¹ Patients with hypomorphic *RAG1/2* variants may also suffer from severe varicella,⁹¹ as may patients with inborn errors affecting the alternative NF- κ B pathway, who also suffer from reactivations.¹⁹² Supporting the hypothesis of a potential role of these auto-Abs in HSV1/2, VZV and/or CMV infections, adverse herpesvirus reactivations in humans have been reported following treatment with JAK inhibitors, which impair IFN immunity through more far-reaching effects not limited to type I IFNs,^{193,194} and in patients treated with an IFNAR-blocker, anifrolumab, who frequently suffer from VZV infections, mostly reactivations (herpes zoster or shingles).^{195–197} Interestingly, auto-Abs neutralizing IFN- α were found in one patient with VZV reactivation causing postherpetic neuralgia (PHN).¹⁹⁸

Some patients with severe reactions to the yellow fever virus live attenuated vaccine (YFV LAV) have been found to have inborn errors of type I immunity or preexisting auto-Abs neutralizing type I IFNs.^{19,22} Indeed, >30% of patients with severe reactions to the YFV LAV have high titers of auto-Abs neutralizing IFN- α 2 and IFN- ω . Furthermore, these auto-Abs can also block type I IFN-mediated protection against YFV-17D infection in vitro. The patients suffered from no prior severe viral infections, but one developed a severe influenza B infection with bilateral interstitial pneumonia 2 years later. Interestingly, one patient was diagnosed with SLE, consistent with the higher risk of viral diseases in SLE patients with auto-Abs against type I IFNs.²² It remains unclear why no adverse reactions have ever been reported in children with auto-Abs against type I IFNs (as in APS-1) vaccinated with the MMR vaccine. As MMR does not cause disease in patients with IRF7 deficiency, residual IFN- β activity may be sufficient to protect against infection in this context, as may type III IFN activity. We then tested the hypothesis that severe infections with wild-type flaviviruses might also be caused by auto-Abs neutralizing type I IFNs. In an international cohort of over 400 patients hospitalized for WNV disease (WNVD), 35% were found to harbor auto-Abs neutralizing IFN- α 2 and/or IFN- ω .¹³⁶ The prevalence of these antibodies was highest in patients with encephalitis (~40%) while, in individuals with asymptomatic WNV infection, it was as low as that in the general population. Strikingly, 22% of the patients had auto-Abs neutralizing high concentrations (10 ng/mL) of both IFN- α 2 and

TABLE 1 Odds ratios for severe disease in patients with auto-Abs neutralizing type I IFNs.

	OR [95% CI]		
	Children under 18 years old	Adults under 65 or 70 years old	Adults over 65 or 70 years old
Critical COVID-19			
IFN- β 10ng/mL	4.9 [0–95.1]		
IFN- α 10ng/mL	40.6 [6.4–429.8]		
IFN- ω 10ng/mL	7.7 [1.8–26.7]		
IFN- α 100pg/mL	28.2 [8.8–101.3]		
IFN- ω 100pg/mL	4.2 [2–7.9]		
IFN- α or IFN- ω 10ng/mL	9.2 [2.6–29.1]	48.1 [34.4–67.2]	7 [5.4–9.0]
IFN- α and IFN- ω 10ng/mL	68 [5.4–9435.4]	160 [69.3–369.3]	13 [8.8–19.3]
IFN- α or IFN- ω 100pg/mL	5.3 [2.8–9.6]	12.3 [9.4–16.0]	5.1 [4.0–6.4]
IFN- α and IFN- ω 100pg/mL	19.4 [4.7–87.8]	184.9 [45.7–748.3]	7 [5.1–9.7]
Critical flu			
IFN- β 10ng/mL	–	1.1 [0.1–19.8]	2.3 [0.1–51]
IFN- α 10ng/mL	–	52.1 [22.3–121.8]	1.8 [0.5–6.3]
IFN- ω 10ng/mL	–	24.9 [9.9–62.4]	1.3 [0.2–6.5]
IFN- α 100pg/mL	–	17.5 [8.4–36.6]	1.1 [0.4–3.3]
IFN- ω 100pg/mL	–	5.5 [2.5–11.9]	0.5 [0.1–2.8]
IFN- α or IFN- ω 10ng/mL	–	23.4 [10.7–51.4]	1.2 [0.3–4.4]
IFN- α and IFN- ω 10ng/mL	–	139.9 [42.3–462.5]	2.5 [0.5–13.1]
IFN- α or IFN- ω 100pg/mL	–	5.7 [3–11.1]	0.8 [0.3–2.4]
IFN- α and IFN- ω 100pg/mL	–	77 [22.4–264.4]	0.9 [0.2–4.8]
WNVD			
IFN- β 10ng/mL	–		
IFN- α 10ng/mL	–	185.6 [96–359]	54.7 [39.8–75]
IFN- ω 10ng/mL	–	139.2 [77.6–249.7]	42.4 [30.2–59.6]
IFN- α 100pg/mL	–	54.8 [29.6–101.6]	28.3 [20.9–38.4]
IFN- ω 100pg/mL	–	25 [15.4–40.6]	28.2 [20.6–38.6]
IFN- α or IFN- ω 10ng/mL	–	80.5 [48.6–133.3]	40.9 [30.5–55]
IFN- α and IFN- ω 10ng/mL	–	558.1 [201.7–1544.1]	82.9 [55.2–124.6]
IFN- α or IFN- ω 100pg/mL	–	16.8 [10.7–26.3]	22.2 [16.7–29.6]
IFN- α and IFN- ω 100pg/mL	–	304.6 [99.4–933.3]	43.9 [30.8–62.5]
WNF			
IFN- β 10ng/mL	–		
IFN- α 10ng/mL	–	78.7 [26.1–237.5]	6.6 [1.9–22.2]
IFN- ω 10ng/mL	–	58.8 [22.3–155.1]	5.4 [1.3–23.2]
IFN- α 100pg/mL	–	30.1 [11.8–76.9]	3.2 [0.9–10.6]
IFN- ω 100pg/mL	–	14.5 [6.9–30.4]	5.2 [1.8–15.2]
IFN- α or IFN- ω 10ng/mL	–	36.2 [15.1–86.3]	4.8 [1.4–16]
IFN- α and IFN- ω 10ng/mL	–	229.1 [53.4–983.7]	11.7 [2.7–51.2]
IFN- α or IFN- ω 100pg/mL	–	11.8 [6–23.1]	3.1 [1.1–9]
IFN- α and IFN- ω 100pg/mL	–	114.4 [27.7–472.5]	6.8 [2–23.1]

Note: The age cutoffs for the cohorts differed: critical COVID-19: 65 years old, critical flu: 65 years old, WNVD: 70 years old, WNF: 70 years old.

IFN- ω , increasing the risk of developing WNVD by a factor of 127.4 (95% CI: 87.1–186.4, $P < 10^{-15}$) (Table 1). Importantly, these auto-Abs were found in the CSF of most (67%) of the subjects with

circulating auto-Abs tested, providing additional evidence of their causal role in neuro-invasiveness. Finally, these auto-Abs blocked the protective antiviral activity of IFN- α 2 against WNV in vitro.

Overall, anti-IFN-I auto-Abs account for 40% of WNV encephalitis cases, making this the best understood human infectious disease to date. These antibodies are probably also involved in other yet unstudied arboviral infections. It is also tempting to speculate that there are inborn errors of type I IFN conferring a predisposition to WNV encephalitis. Auto-Abs neutralizing type I IFNs, thus, underlie many of the severe viral infections seen in patients with inborn errors of type I IFN and several infections not yet observed in such patients.

7 | CONCLUDING REMARKS

The detection of auto-Abs neutralizing type I IFNs has important direct clinical implications for the diagnosis, management, and follow-up of patients. Assuming that there are no major ethnic or geographic differences, we can estimate that about 100 to 200 million people worldwide have auto-Abs capable of neutralizing type I IFNs (for a conservative prevalence of 0.5% in individuals under 65 years of age and 5% in those over 70 years of age). Targeted population screening (i.e., in the elderly or individuals with a history of severe viral or autoimmune disease) would be of interest to identify positive individuals and prevent severe viral infections. Antiviral drugs can be used when available (i.e., acyclovir in case of HSV1/2 or VZV infection; valganciclovir in case of CMV infection; oseltamivir in case of influenza infection; IFN- β ,¹⁹⁹ nirmatrelvir plus ritonavir, remdesivir and molnupiravir, monoclonal Abs in the context of COVID-19 infection). IFN- λ is of particular interest for COVID-19,²⁰⁰ and perhaps also influenza. For efficacy, these treatments should be administered early in the course of infection, before the hyperinflammatory syndrome has begun. In cases of very severe clinical presentation, a combination of several treatments, including antiviral drugs and treatments for removing the auto-Abs (plasmapheresis), could be used as rescue measures.^{138,199}

These auto-Abs are common, strong, universal determinants of viral infections in humans. The odds ratios of between 10 and 100 obtained are unprecedented, particularly in so many people and at such an international scale. They underlie at least five life-threatening rare or common viral infections. Other viral illnesses, including viral infections of the brain and respiratory tract in particular, may be caused by auto-Abs against type I IFNs. Viral diseases with a particular impact on the elderly are prime candidates. With age, antiviral immunity may diminish, perhaps in part because of the decrease in naïve T cells secondary to thymic involution, and the exhaustion of memory T cells. Auto-Abs neutralizing type I IFNs may worsen the clinical consequences of declining T- and B-cell immunity to viruses. It is also tempting to speculate that auto-Abs against type I IFNs may underlie or contribute to the development of certain cancers. In the 1980s, several teams reported a direct effect of type I IFNs, inhibiting cancer growth.²⁰¹⁻²⁰³ Type I IFNs were even reported to be curative in patients with hairy cell leukemia²⁰⁴ or Kaposi sarcoma.^{205,206} IFN- ϵ was recently found to be tumor suppressor.⁶⁸ An impact of type I IFNs was also described in the response

to treatment, including immunomodulatory treatment.^{207,208} An appealing hypothesis is that the emergence of auto-Abs against type I IFNs with age might modulate the anti-tumor effects of type I IFNs.^{208,209} Further explorations are required to determine the full range of predisposition to viral and malignant conditions conferred by auto-Abs neutralizing type I IFNs, as these antibodies may have a major effect on public health.

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CONFLICT OF INTEREST STATEMENT

J.-L.C. reports being an inventor on patent application PCT/US2021/042741, filed 22 July 2021, submitted by The Rockefeller University, which covers the diagnosis of, susceptibility to, and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. The other authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

All data is available upon request to the corresponding authors.

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