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Abstract: The type I IFN (IFN-I) system is essential to limit severe viral disease in humans. Thus, IFN-I deficiencies are associated with serious life-threatening infections. Remarkably, some rare individuals with chronic autoimmune diseases develop neutralizing autoantibodies (autoAbs) against IFN-Is thereby compromising their own innate antiviral defenses. Furthermore, the prevalence of anti-IFN-I autoAbs in apparently healthy individuals increases with age, such that ~4% of those over 70 years old are affected. Here, I review the literature on factors that may predispose individuals to develop anti-IFN-I autoAbs, such as reduced self-tolerance caused by defects in the genes AIRE, NFKB2, and FOXP3 (among others), or by generally impaired thymus function, including thymic involution in the elderly. In addition, I discuss the hypothesis that predisposed individuals develop anti-IFN-I autoAbs following "autoimmunization" with IFN-Is generated during some acute viral infections, systemic inflammatory events, or chronic IFN-I exposure. Finally, I highlight the enhanced susceptibility that individuals with anti-IFN-I autoAbs appear to have towards viral diseases such as severe COVID-19, influenza, or herpes (e.g., varicella-zoster virus, herpes simplex virus, cytomegalovirus), as well as adverse reactions to live-attenuated vaccines. Understanding the mechanisms underlying development and consequences of anti-IFN-I autoAbs will be key to implementing effective prophylactic and therapeutic measures.

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HIGHLIGHTS

Basic

REVIEW

Autoantibodies targeting type I interferons: Prevalence, mechanisms of induction, and association with viral disease susceptibility

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The type I IFN (IFN-I) system is essential to limit severe viral disease in humans. Thus, IFN-I deficiencies are associated with serious life-threatening infections. Remarkably, some rare individuals with chronic autoimmune diseases develop neutralizing autoantibodies (autoAbs) against IFN-Is thereby compromising their own innate antiviral defenses. Furthermore, the prevalence of anti-IFN-I autoAbs in apparently healthy individuals increases with age, such that ~4% of those over 70 years old are affected. Here, I review the literature on factors that may predispose individuals to develop anti-IFN-I autoAbs, such as reduced self-tolerance caused by defects in the genes *AIRE*, *NFKB2*, and *FOXP3* (among others), or by generally impaired thymus function, including thymic involution in the elderly. In addition, I discuss the hypothesis that predisposed individuals develop anti-IFN-I autoAbs following "autoimmunization" with IFN-Is generated during some acute viral infections, systemic inflammatory events, or chronic IFN-I exposure. Finally, I highlight the enhanced susceptibility that individuals with anti-IFN-I autoAbs appear to have towards viral diseases such as severe COVID-19, influenza, or herpes (e.g., varicella-zoster virus, herpes simplex virus, cytomegalovirus), as well as adverse reactions to live-attenuated vaccines. Understanding the mechanisms underlying development and consequences of anti-IFN-I autoAbs will be key to implementing effective prophylactic and therapeutic measures.

Keywords: autoantibodies · autoimmunity · interferon · self-tolerance · viral disease

Introduction

The human type I IFN (IFN-I) system is a critical first-line component of host innate immune defences. In response to most viral infections, cells secrete soluble IFN-I cytokines that bind to specific receptors on nearby cells and trigger the induction of many hundreds of antivirally-active IFN-stimulated genes (ISGs). Together, these ISGs create a powerful and broadly protective state that limits further virus spread (reviewed in [1]).

Genetic deficiencies that compromise the IFN-I system are strongly associated with the development of severe, life-threatening, viral disease in humans, thus these deficiencies are extremely rare (reviewed in [2–4]). In this context, a striking observation made during the COVID-19 pandemic was that a notable proportion of elderly individuals appear to possess autoantibodies (autoAbs) that are able to bind to, and inhibit the function of, their own IFN-I cytokines [5], and immunocompromisation caused by such anti-IFN-I autoAbs can correlate with severe viral disease [6]. While anti-IFN-I autoAbs have been recognized in humans for more than 40 years, they were typically only identified sporadically (e.g. [7–9]), or studied extensively in specific patient groups with rare autoimmune diseases (e.g. [10–12]). Thus, the relatively new association of anti-IFN-I autoAbs

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with severe viral disease in previously healthy individuals, and the updated estimates regarding their prevalence in the general human population, have sparked a renewed interest in this field from the infectious disease community.

Here, I review the literature on anti-IFN-I autoAbs and attempt to integrate the surge of recent findings on this topic with past work. I focus on discussing critical concepts relating to how anti-IFN-I autoAbs might develop in individuals due to genetic, constitutional, and environmental factors, and how anti-IFN-I autoAbs might lead to increased viral disease susceptibility. In addition, I highlight open questions relating to possible physiological roles for anti-IFN-I autoAbs, the unresolved specificity/selectivity of this phenomenon, and the future application of knowledge in this area to guide diagnostic and therapeutic regimens.

Which individuals possess anti-IFN-I autoAbs?

In humans, the IFN-I cytokines are comprised of multiple subtypes of IFN-α, as well as the closely related IFN-ω, IFN-β, and a few other IFNs [1]. Naturally occurring anti-IFN-I autoAbs have mainly been described to bind the IFN-α subtypes and/or IFN-ω, while autoAbs against IFN-β and other IFNs appear to be much rarer [5]. The basis and consequence of this selectivity are enigmatic and have not yet been fully addressed. Thus, future investigations on this important topic may reveal new biological insights and properties associated with individual IFNs. However, for the purposes of the general concepts discussed in this review, I will for the most part not discriminate between specific anti-IFN-I autoAbs.

Overall, anti-IFN-I autoAbs are uncommon in apparently healthy members of the general human population, although estimates of their prevalence and levels can vary [5, 13, 14]. In the largest and most recent cross-sectional study that included samples from nearly 35,000 people, only around 0.2-1% of those under 70 years of age had detectable anti-IFN-I autoAbs, but this increased markedly to 1–2% of those between 70 and 80, and to 3–6% of those over 80, although after 85 there was a small decrease in prevalence [5]. Furthermore, there appears to be a slightly higher prevalence of these autoAbs in elderly men (aged 70–80 years old) than in elderly women [5]. Thus, a fraction of the elderly population harbor anti-IFN-I autoAbs and might therefore be considered at least partially immunocompromised.

In contrast, anti-IFN-I autoAbs have been described in a significant proportion of patients of all ages with specific chronic autoimmune or autoimmune-related diseases, including systemic lupus erythematosus (SLE) [9, 11, 12, 15], autoimmune polyendocrinopathy syndrome type 1 (APS-1) [10], Sjögren's syndrome (SS) [12, 16], late-onset (or thymoma-triggered) myasthenia gravis [11], immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome [17], and psoriasis or pemphigus foliaceus [18, 19]. Anti-IFN-I autoAbs have also been reported to develop in a fraction of patients suffering from incontinentia pigmenti [6], myeloproliferative neoplasms [20], thymoma [11, 21, 22], chronic graft-versus-host disease following allogeneic bone marrow transplantation [23, 24], chronic viral hepatitis [24], and primary immunodeficiencies such as Omenn syndrome, Leaky SCID (Severe Combined Immunodeficiency), T-cell lymphopenia, or combined immunodeficiency with granulomatous disease and/or autoimmunity (CID-G/AI) [25]. Notably, in some autoimmune diseases where elevated levels of IFN-I are implicated in maintaining clinical symptoms [16, 26, 27], possession of anti-IFN-I autoAbs appears to ameliorate the disease. For example, the progressive natural development of anti-IFN-I autoAbs in a subset of SLE patients reduces functional IFN-I levels and thereby exerts a dampening effect on SLE [12, 15, 28, 29]. Similarly, it has been reported that APS-1 patients with high-affinity anti-IFN-I autoAbs have a degree of protection against type I diabetes [27], and SS patients with such autoAbs may also have reduced clinical symptoms [16]. Thus, vaccination with an inactivated IFN-I, IFN-kinoid, to induce therapeutic anti-IFN-I antibodies has been trialed in some patients with SLE [30].

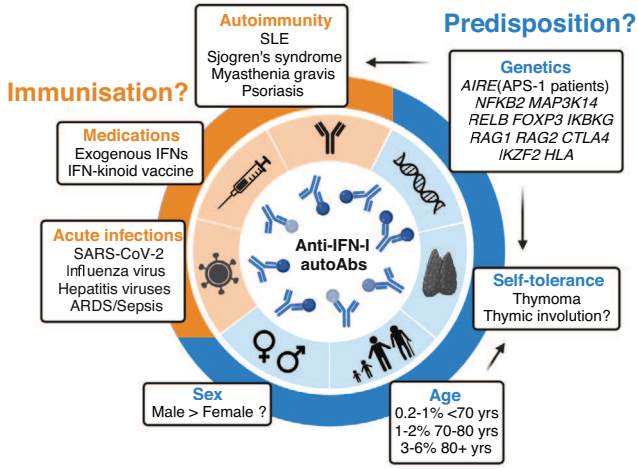

Figure 1. Factors associated with the development of anti-IFN-I autoAbs. Schematic overview of a 'two-hit' hypothesis of predisposing factors and (auto) immunizing factors associated with the development of anti-IFN-I autoAbs. Predisposing factors, such as mutations in specific genes (genetics), loss of self-tolerance (e.g. reduced thymus function), age, and sex are depicted in blue, together with the interdependencies they share (arrows). Immunizing factors that may lead to high or chronic levels of IFN-I, such as acute infections, IFN-I treatments, or some chronic autoimmune diseases are depicted in orange. Abbreviations: APS-1, autoimmune polyendocrinopathy syndrome type 1; SLE, systemic lupus erythematosus; ARDS, acute respiratory distress syndrome; IFN, interferon; autoAbs, autoantibodies. Figure created with BioRender.com.

How do anti-IFN-I autoAbs develop: role of the thymus, self-tolerance, and genetics?

Under normal circumstances, the body should not develop antibodies against self-antigens. As such, the increased frequency of anti-IFN-I autoAbs in a number of specific diseases with defined genetic etiologies gives strong clues as to important factors that likely contribute to their abnormal development (Fig. 1).

Notably, many of these patient groups have defects in genes that are responsible for self-tolerance (i.e., limiting autoimmune responses), most strikingly with regard to thymic selection. For example, APS-1 patients harbor loss-of-function mutations in *AIRE*, which encodes an autoimmune regulator. The AIRE protein is a transcriptional activator usually highly expressed in medullary thymic epithelial cells where it functions to promote expression of tissue-specific self-antigens and thus allows maintenance of self-tolerance in the thymus by ensuring negative selection of autoreactive T-cells [31]. Defective AIRE therefore leads to loss of tolerance, and autoreactivity directed towards self-antigens, which includes a poorly understood dominance towards IFN-Is (particularly IFN-α/IFN-ω). Furthermore, genetic mutations in *NFKB2*, as well as other non-canonical NF-κB pathway genes (such as *MAP3K14* (NIK) and *RELB*), have recently been identified in a number of patients who developed anti-IFN-I autoAbs [32–37]. Interestingly, *NFKB2* is required for the correct expression of *AIRE* [38], and patients with defects in these non-canonical NF-κB pathway genes have a lower thymic expression of *AIRE* [37], again likely impacting the establishment of self-tolerance and promoting development of autoAbs, including those against IFN-Is. A similar picture is noted in patients with mutations in *RAG1/RAG2*, who have a high prevalence of anti-IFN-I autoAbs [25], and who exhibit a disorganized thymus lacking *AIRE* expression in medullary thymic epithelial cells [39, 40]. Along this theme, mutations in other genes that may impact different aspects of self-tolerance, the canonical NF-κB pathway, or B-cell/T-cell function have also been identified in patient cohorts with anti-IFN-I autoAbs, including *FOXP3* [17], *IKBKG* (NEMO) [6], *CTLA4* [36], and *IKZF2* [36, 41]. In addition, there is some evidence that specific *HLA* alleles and genetic variants can predispose to developing high-titer anti-IFN-I autoAbs (at least against IFN-β) in patients treated with IFN-β [42–44], which could relate to the resulting MHC class II molecules mis-presenting IFN-I-derived immunopeptides during the self-tolerance selection process. Thus, an overall picture is emerging where genetic dysregulation of normal self-tolerance, particularly with regard to thymus function, is highly associated with development of anti-IFN-I autoAbs. Rare variants in other human genes, including in genes with known immuno-regulatory properties, have also been detected sporadically in patients with anti-IFN-I autoAbs [36, 42], and a somatic gain-of-function mutation in *JAK2* may have a protective role against the development of anti-IFN-I autoAbs under certain circumstances [20]. It will be critical to determine the spectrum of genetic susceptibility traits, either in tolerance-related genes or other currently-unappreciated pathways, that associate with development of anti-IFN-I autoAbs.

The importance of disrupted thymic function in the development of anti-IFN-I autoAbs is also underlined by the observation that most thymoma patients, who often harbor these autoAbs, have undetectable levels of *AIRE* expression in their thymoma tissue, despite normal *AIRE* expression in non-neoplastic tissue [45]. Furthermore, anti-IFN-I autoAbs increase in prevalence with age [5], and thymic involution (or shrinking) is a naturally occurring part of the aging process that leads to reduced thymus activity and increased likelihood of high autoimmune incidence [46]. Interestingly, the rate of thymic involution can be regulated by numerous growth hormones and sex steroids, as well as by metabolic activity, and involution appears to occur more rapidly in males than females [46]. It is therefore tempting to speculate that constitutional factors correlating with reduced thymus activity, including some cancers, age, sex, or certain other diseases/disorders and lifestyles, could increase individual risk of developing anti-IFN-I autoAbs (Fig. 1).

How do anti-IFN-I autoAbs develop: Role of environmental triggers?

While reduced self-tolerance through genetic or constitutional mechanisms correlates with anti-IFN-I autoAb development, it is probably not sufficient. For example, while APS-1 patients almost all have anti-IFN-I (IFN-α/IFN-ω, but rarely IFN-β) autoAbs at high levels during infancy, the autoAbs are not necessarily present at birth, and thus perhaps only develop in the first few months or years of life [10, 47, 48]. In addition, only 60% of thymoma patients [45], and 4% of the elderly [5], have anti-IFN-I autoAbs. One might therefore speculate that self-tolerance breakdown alone does not lead in itself to production of anti-IFN-I autoAbs, but is a predisposing factor that requires a second event that might differ between individuals or groups of people. Such a second event would be the "autoimmunization" process with IFN-Is.

Development of anti-IFN-I autoAbs has been recognized to occur rarely in some individuals who were treated with exogenous human IFN-I for cancers, multiple sclerosis (MS), or chronic viral infections [8, 49-55]. This suggests that human IFN-Is can be immunogenic, although this is clearly an atypical situation as only some patients raise anti-IFN-I autoAbs [8, 49–53] even if multiple individuals are administered with the same preparation and dose of IFN-I [49]. Furthermore, anti-IFN-I autoAbs induced by IFN-I treatment have been reported to mostly appear transiently, and last between a few months or years despite ongoing IFN-I administration [51, 53, 56]. Acute viral infections and systemic inflammation are also potential triggers for the production of high amounts of endogenous IFN-Is. Consequently, anti-IFN-I autoAbs have been reported in several of these situations, for example with acute HIV-1, SARS-CoV-2, influenza virus, and hepatitis A, B, or C virus infections [11, 57-63], with a potentially IFN-stimulating vaccine dose [64], and during acute respiratory distress syndrome or severe sepsis [65] (Fig. 1). Acute viral infections in general can trigger autoAbs against a range of IFN and non-IFN molecules [60, 61, 66]. While levels of such induced autoAbs probably naturally decline after a few months [56, 59, 62], some rare individuals exposed to IFN-I have been described to remain positive for anti-IFN-I autoAbs for many years [56, 67]. Thus, environments where relatively large amounts of IFN-I antigen are present (e.g. acute infections, hyper-inflammatory situations, IFN-I treatment regimens), or environments where IFN-I is produced chronically (e.g. 'interferonopathies', autoimmune diseases, some cancers),

might trigger low-level and self-resolving anti-IFN-I autoAbs that have as yet unidentified physiological regulatory functions, such as dampening inflammatory responses. However, in individuals additionally suffering from poor self-tolerance, it is possible that this resolution does not occur, and anti-IFN-I autoAbs develop to high levels and/or are maintained for longer. Indeed, it has been shown experimentally that repeated innate immune stimulation with virus-like IFN-agonists in partially immunodeficient mice (hypomorphic *Rag1*) leads to the development of broad-spectrum autoAbs (albeit anti-IFN-I autoAbs were not detected) [25]. The requirement for an infectious, or IFN-inducing, trigger for anti-IFN-I autoAbs in those with thymic dysfunction could still fit with the extremely high penetrance of this phenotype in APS-1 patients (100%), who have compromised self-tolerance from birth, as like all children they are likely to encounter multiple common IFN-inducing acute viral infections at very early ages before they have established specific anti-pathogen humoral immunity. In contrast, older individuals who develop thymic decline over their lifetime may be less likely to experience high IFN-inducing acute infections because cells from aged individuals generally produce less IFN-I following stimulation [68], and these individuals have a degree of anti-pathogen protection from pre-existing humoral immunity. This could explain why the development of anti-IFN-I autoAbs in elderly cohorts is rarer (4%) as compared to APS-1 cohorts (100%).

In support of the speculations above, several cohorts of individuals who have been shown to develop anti-IFN-I autoAbs are known to experience high or chronic IFN-I environments where IFN-I "autoimmunization" is possible (Fig. 1). As already discussed, the most notable examples are individuals with SLE or SS [16, 26]. In addition, high levels of IFN-I may be produced chronically during chronic graft-versus-host disease following allogeneic bone marrow transplantation [69], and chronic IFN-I is a known inducer or aggravator of the inflammatory skin disease, psoriasis [70], both diseases where anti-IFN-I autoAbs have been detected [18, 23, 24]. Furthermore, ataxia-telangiectasia might be classified as an 'interferonopathy' based on the elevated chronic expression of IFN-I that associates with this disease [71], and at least one ataxia-telangiectasia patient has been described to possess anti-IFN-I autoAbs [25]. Many factors, including those discussed above relating to the thymus, could have plausibly contributed to a breakdown in self-tolerance that allowed some individuals suffering from these diseases to induce anti-IFN-I autoAbs. In addition, IFN-I itself may also have played a contributing role in breaking tolerance, as IFN-I treatment of B-cells has been reported to protect them from B-cell receptor-mediated apoptosis, which would allow self-reactive B-cells to escape negative selection [72]. Indeed, B-cell expression of the receptor for IFN-I has been shown to be required for development of some autoAbs in a mouse model of SLE [73]. It will be important in the future to develop refined *in vivo* models that can recapitulate the induction of anti-IFN-I autoantibodies in order to understand fully the predispositions and triggers involved, as well as possible disease consequences. In this regard, it is interesting to note that sporadic reports have described anti-IFN-I autoAbs occurring spontaneously in some strains of laboratory mice and rats at low levels, with prevalence and titers appearing to increase slightly with age [74, 75]. This situation appears analogous to that in humans [5], and may warrant further investigation to uncover potential similarities and differences between anti-IFN-I autoAb induction in these species.

How do anti-IFN-I autoAbs associate with viral disease susceptibility?

Given that monogenic defects in the human IFN-I system can lead to increased susceptibility to severe viral diseases [3, 4], the functional neutralization of IFN-I in individuals with pre-existing anti-IFN-I autoAbs is also likely to exacerbate the severity of an infection. Indeed, this was first suspected in the atypical case of an otherwise healthy and apparently immunocompetent 77-year-old female who suffered from an episode of disseminated herpes zoster caused by reactivation of latent varicella-zoster virus (VZV), and whose serum at the time of disease contained anti-IFN-I autoAbs [7, 76]. More recently, in a comparative study, a higher incidence of anti-IFN-I autoAbs was found in patients suffering from postherpetic neuralgia (a painful but infrequent severe consequence of VZV reactivation) than in patients with typical herpes zoster [77], implicating an association of anti-IFN-I autoAbs with severe disease. Similar associations have since been made with other viral diseases, as anti-IFN-I autoAbs can be found in around 10–20% of critically ill COVID-19 patients (first described in [6], and replicated in [63, 66, 78-86] among others), and in around 5% of critically-ill influenza patients [87], but are not generally found in individuals with mild infections. Critically ill COVID-19 patients with anti-IFN-I autoAbs have also been noted to have an increased risk of developing herpesvirus disease (herpes simplex virus, HSV; or cytomegalovirus, CMV), as compared to similarly ill COVID-19 patients without anti-IFN-I autoAbs [83]. As such, presence of anti-IFN-I autoAbs appears to be a major correlate of COVID-19-associated mortality [5, 88], as well as a correlate of severe influenza in some individuals [87]. In addition, anti-IFN-I autoAbs have been associated with severe adverse reactions to the live-attenuated yellow fever vaccine [25, 89], and may have been involved in a possible persistent infection with parvovirus B19 in an elderly male [90] (Fig. 2).

The above examples looked for anti-IFN-I autoAbs in cases with atypical severe viral disease, but given the possibility that acute viral infections might trigger low-level and self-resolving autoAbs [59, 60, 62], it is difficult to state directly that the anti-IFN-I autoAbs preceded and exacerbated the infection. Nevertheless, in a number of individuals anti-IFN-I autoAbs have been identified prior to the development of severe viral disease, and the anti-IFN-I autoAbs detected soon after acute infection were already apparent high-affinity IgG, and not IgM, strongly suggesting their pre-existence [6]. Furthermore, complementary observations have been made that focused on patients known to have high serum levels of anti-IFN-I autoAbs from early ages. For example, APS-1 patients were found to experience more severe primary infections with VZV and herpes simplex virus (HSV), and to

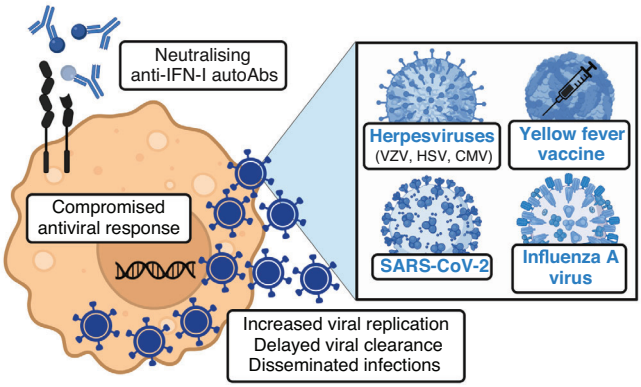

Figure 2. Association of anti-IFN-I autoAbs with viral disease susceptibility. Simplified schematic representation of the mechanism by which neutralizing anti-IFN-I autoAbs prevent binding of IFN-Is to the IFN receptor and thereby limit ISG expression and antiviral activity. Examples of viral infections exacerbated by anti-IFN-I autoAbs are depicted. Abbreviations: VZV, varicella-zoster virus; HSV, herpes simplex virus; CMV, cytomegalovirus; IFN, interferon; autoAbs, autoantibodies. Figure created with BioRender.com.

exhibit herpes zoster reactivations more frequently (and at earlier ages) than non-APS-1 patients [91]. Some (but not all [92]) APS-1 patients have also been described to be at high risk of developing severe COVID-19 [93, 94]. Similarly, thymoma and SLE patients who develop anti-IFN-I autoAbs have been shown to have a clear predisposition to viral diseases such as herpes zoster and severe COVID-19 [15, 22]. Furthermore, individuals with immune dysfunctions caused by hypomorphic mutations in *RAG1/RAG2*, and thereby suffering from diseases such as Omenn syndrome, Leaky SCID, T-cell lymphopenia, or CID-G/AI, have also been identified with anti-IFN-I autoAbs at early ages, and such patients had a higher propensity of severe or disseminated viral infections caused by VZV, CMV or adenovirus [25]. The recognized spectrum of infectious diseases whose severity is enhanced by pre-existing anti-IFN-I autoAbs is likely to increase dramatically with further research in this area.

The ability of anti-IFN-I autoAbs to block (neutralize) soluble IFN-Is from binding to their receptor on the surface of cells, thereby preventing upregulation of antiviral ISGs, is the most straightforward mechanism by which these autoAbs could promote virus replication and subsequent disease (Fig. 2). Indeed, while anti-IFN-I autoAbs have been detected that are either neutralizing or non-neutralizing, it is generally only neutralizing anti-IFN-I autoAbs that are associated with severe viral infections [5, 15, 87, 88, 95, 96], and the more IFN-I subtypes (e.g. α, β, ω) neutralized the greater the severity [15, 88]. Presence of local neutralizing anti-IFN-I autoAbs in mucosa has therefore been correlated with increased viral loads and delayed viral clearance during SARS-CoV-2 infections [66, 83, 95, 97] (Fig. 2). While high amounts of anti-IFN-I autoAbs may be required to neutralize the IFN-I generated during acute infections, thus making systemic and local levels of functional IFN-I (and consequently systemic and local levels of ISGs) low or undetectable in many patients with anti-IFN-I autoAbs [5, 6, 63, 82, 97, 98], it is possible that low amounts of neutralizing anti-IFN-I autoAbs can also exert important virus exacerbating effects. For example, reduced levels of baseline ISGs have been measured in circulating immune cells from uninfected patients with APS-1 [99], likely due to their anti-IFN-I autoAbs neutralizing the very small amount of tonic IFN-I required to continuously prime antiviral responses. Thus, individuals with even low amounts of anti-IFN-I autoAbs might have a generally increased susceptibility to infection as their baseline levels of antiviral defenses, and consequently their ability to respond rapidly to an invading exogenous pathogen, will be compromised.

Concluding remarks

Much remains to be clarified about the possible 'two-hit'-mediated development of anti-IFN-I autoAbs, particularly with regard to the role of predisposing host genetics or constitutional factors (e.g., thymic status, age, sex, diseases) as well as potential "autoimmunization" triggers (e.g., some infections or unusual inflammatory scenarios). Understanding these processes in more detail will be critical to identify (and mitigate) risks associated with acquiring this type of immunodeficiency, particularly in the elderly. At another level, and not discussed in detail in this review, the higher prevalence of autoAbs targeting IFN-α subtypes and/or IFN-ω, as compared to rare autoAbs targeting IFN-β or even other IFN types, such as IFN-III (λ) [5, 6, 10, 85], is a highly intriguing phenomenon, and studies in this area to uncover the biological basis and pathophysiology of this apparently selective mechanism are certainly warranted. While the relative levels of certain IFNs during "autoimmunization" or their potential differential presentation by MHC-II could play important roles, an analogous mechanism to the induction of anti-IFNγ autoAbs by a fungal pathogen via 'molecular mimicry' cannot be excluded [100]. Either way, the specific disease consequences for the extremely rare individuals who do develop autoAbs against IFN-β or IFN-λ should be investigated.

Despite the strong association between general possession of anti-IFN-I autoAbs and severe viral infections, it remains to be determined whether there might be a normal physiological role for low-level, transient, development of anti-IFN-I autoAbs that act to dampen certain inflammatory states, particularly given the observed widespread and fluctuating instances of these autoAbs during many acute viral infections [11, 57-63]. While some individuals may then go on to aberrantly maintain anti-IFN-I autoAbs in their blood and be highly susceptible to severe viral disease, the precise levels of these autoAbs and the IFN-I subtypes/epitopes that they must target to effectively compromise innate antiviral immunity still need to be dissected in order to define a clear 'correlate of susceptibility'. In the longer term, such a 'correlate of susceptibility' would be necessary before embarking on the development of advanced treatments that might be designed to target specific pathogenic autoAbs. In the shorter term, a 'correlate of susceptibility' would be useful for effective early diagnosis of individuals with the most dangerous constellations of anti-IFN-I autoAbs, who could immediately be prioritized for prophylactic vaccination regimens (using non-live vaccines) or other risk

mitigation measures. Indeed, individuals with anti-IFN-I autoAbs are still able to mount efficient humoral responses to vaccines [101], though breakthrough infections can occur [102]. Furthermore, treatment strategies for those with critical viral illness and anti-IFN-I autoAbs could include highly invasive plasma exchange therapies to remove autoAbs from circulation [93, 103], B-cell depletion therapies [104], or treatments with antiviral IFN-Is that are not targeted by patient autoAbs (e.g. IFN-β or potentially IFN-λ) [105, 106], although this latter strategy could risk the development of new anti-IFN-β/λ autoAbs in susceptible patients. Thus, future definition of a 'correlate of susceptibility', and its application to patient diagnosis, should refine the classification of patients requiring specific treatment.

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References

1 **Mesev, E. V., LeDesma, R. A. and Ploss, A.**, Decoding type I and III interferon signalling during viral infection. *Nat. Microbiol.* 2019. **4**: 914–924.

2 **Stertz, S. and Hale, B. G.**, Interferon system deficiencies exacerbating severe pandemic virus infections. *Trends Microbiol.* 2021. **29**: 973–982.

3 **Meyts, I. and Casanova, J. L.**, Viral infections in humans and mice with genetic deficiencies of the type I IFN response pathway. *Eur. J. Immunol.* 2021. **51**: 1039–1061.

4 **Duncan, C. J. A., Randall, R. E. and Hambleton, S.**, Genetic lesions of type I interferon signalling in human antiviral immunity. *Trends Genet.* 2021. **37**: 46–58.

5 **Bastard, P., Gervais, A., Le Voyer, T., Rosain, J., Philippot, Q., Manry, J., Michailidis, E. et al.**, Autoantibodies neutralizing type I IFNs are present in ∼4% of uninfected individuals over 70 years old and account for ∼20% of COVID-19 deaths. *Sci. Immunol.* 2021. **6**.

6 **Bastard, P., Rosen, L. B., Zhang, Q., Michailidis, E., Hoffmann, H. H., Zhang, Y., Dorgham, K. et al.**, Group, N.-U. I. R. t. C., Amsterdam, U. M. C. C.-B., Effort, C. H. G. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020. 370.

7 **Mogensen, K. E., Daubas, P., Gresser, I., Sereni, D. and Varet, B.**, Patient with circulating antibodies to alpha-interferon. *Lancet* 1981. **2**: 1227–1228.

8 **Vallbracht, A., Treuner, J., Flehmig, B., Joester, K. E. and Niethammer, D.**, Interferon-neutralizing antibodies in a patient treated with human fibroblast interferon. *Nature* 1981. **289**: 496–497.

9 **Panem, S., Check, I. J., Henriksen, D. and Vilcek, J.**, Antibodies to alpha-interferon in a patient with systemic lupus erythematosus. *J. Immunol.* 1982. **129**: 1–3.

10 **Meager, A., Visvalingam, K., Peterson, P., Moll, K., Murumagi, A., Krohn, K., Eskelin, P. et al.**, Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Med.* 2006. **3**: e289.

11 **Meager, A., Wadhwa, M., Dilger, P., Bird, C., Thorpe, R., Newsom-Davis, J. and Willcox, N.**, Anti-cytokine autoantibodies in autoimmunity: preponderance of neutralizing autoantibodies against interferon-alpha, interferon-omega and interleukin-12 in patients with thymoma and/or myasthenia gravis. *Clin. Exp. Immunol.* 2003. **132**: 128–136.

12 **Gupta, S., Tatouli, I. P., Rosen, L. B., Hasni, S., Alevizos, I., Manna, Z. G., Rivera, J. et al.**, Distinct functions of autoantibodies against interferon in systemic lupus erythematosus: a comprehensive analysis of anticytokine autoantibodies in common rheumatic diseases. *Arthritis Rheumatol.* 2016. **68**: 1677–1687.

13 **Ross, C., Hansen, M. B., Schyberg, T. and Berg, K.**, Autoantibodies to crude human leucocyte interferon (IFN), native human IFN, recombinant human IFN-alpha 2b and human IFN-gamma in healthy blood donors. *Clin. Exp. Immunol.* 1990. **82**: 57–62.

14 **Ibrahim, E. H.**, Anti-IFN autoantibodies are present in healthy Egyptian blood donors at low titer. *Cell. Immunol.* 2011. **271**: 365–370.

15 **Mathian, A., Breillat, P., Dorgham, K., Bastard, P., Charre, C., Lhote, R., Quentric, P. et al.**, Lower disease activity but higher risk of severe COVID-19 and herpes zoster in patients with systemic lupus erythematosus with pre-existing autoantibodies neutralising IFN-alpha. *Ann. Rheum. Dis.* 2022. **81**: 1695–1703.

16 **Burbelo, P. D., Browne, S., Holland, S. M., Iadarola, M. J. and Alevizos, I.**, Clinical features of Sjogren's syndrome patients with autoantibodies against interferons. *Clin. Transl. Med.* 2019. **8**: 1.

17 **Rosenberg, J. M., Maccari, M. E., Barzaghi, F., Allenspach, E. J., Pignata, C., Weber, G., Torgerson, T. R. et al.**, Neutralizing anti-cytokine autoantibodies against interferon-alpha in immunodysregulation polyendocrinopathy enteropathy X-linked. *Front. Immunol.* 2018. **9**: 544.

18 **Bergman, R., Ramon, M., Wildbaum, G., Avitan-Hersh, E., Mayer, E., Shemer, A. and Karin, N.**, Psoriasis patients generate increased serum levels of autoantibodies to tumor necrosis factor-alpha and interferon-alpha. *J. Dermatol. Sci.* 2009. **56**: 163–167.

19 **Prummer, O., Zillikens, D. and Porzsolt, F.**, High-titer interferon-alpha antibodies in a patient with pemphigus foliaceus. *Exp. Dermatol.* 1996. **5**: 213–217.

20 **Borsani, O., Bastard, P., Rosain, J., Gervais, A., Sant'Antonio, E., Vanni, D., Casetti, I. C. et al.**, Autoantibodies against type I IFNs in patients with Ph-negative myeloproliferative neoplasms. *Blood* 2022. **139**: 2716–2720.

21 **Meager, A., Vincent, A., Newsom-Davis, J. and Willcox, N.**, Spontaneous neutralising antibodies to interferon–alpha and interleukin-12 in thymoma-associated autoimmune disease. *Lancet* 1997. **350**: 1596–1597.

22 **Burbelo, P. D., Browne, S. K., Sampaio, E. P., Giaccone, G., Zaman, R., Kristosturyan, E., Rajan, A. et al.**, Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. *Blood* 2010. **116**: 4848–4858.

23 **Prummer, O., Bunjes, D., Wiesneth, M., Arnold, R., Porzsolt, F. and Heimpel, H.**, High-titre interferon-alpha antibodies in a patient with chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1994. **14**: 483–486.

24 **Prummer, O., Bunjes, D., Wiesneth, M., Hertenstein, B., Arnold, R., Porzsolt, F. and Heimpel, H.**, Antibodies to interferon-alpha: a novel type of autoantibody occurring after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1996. **17**: 617–623.

25 **Walter, J. E., Rosen, L. B., Csomos, K., Rosenberg, J. M., Mathew, D., Keszei, M., Ujhazi, B. et al.**, Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. *J. Clin. Invest.* 2015. **125**: 4135–4148.

26 **Ronnblom, L. and Alm, G. V.**, An etiopathogenic role for the type I IFN system in SLE. *Trends Immunol.* 2001. **22**: 427–431.

27 **Meyer, S., Woodward, M., Hertel, C., Vlaicu, P., Haque, Y., Karner, J., Macagno, A. et al.**, AIRE-deficient patients harbor unique high-affinity disease-ameliorating autoantibodies. *Cell* 2016. **166**: 582–595.

28 **Morimoto, A. M., Flesher, D. T., Yang, J., Wolslegel, K., Wang, X., Brady, A., Abbas, A. R. et al.**, Association of endogenous anti-interferon-alpha autoantibodies with decreased interferon-pathway and disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2011. **63**: 2407–2415.

29 **Bradford, H. F., Haljasmagi, L., Menon, M., McDonnell, T. C. R., Sarekannu, K., Vanker, M., Peterson, P.** et al. Inactive disease in patients with lupus is linked to autoantibodies to type I interferons that normalize blood IFNalpha and B cell subsets. *Cell Rep. Med.* 2023. **4**: 100894.

30 **Houssiau, F. A., Thanou, A., Mazur, M., Ramiterre, E., Gomez Mora, D. A., Misterska-Skora, M., Perich-Campos, R. A.** et al. IFN-alpha kinoid in systemic lupus erythematosus: results from a phase IIb, randomised, placebo-controlled study. *Ann. Rheum. Dis.* 2020. **79**: 347–355.

31 **Perniola, R.**, Twenty years of AIRE. *Front. Immunol.* 2018. **9**: 98.

32 **Abolhassani, H., Delavari, S., Landegren, N., Shokri, S., Bastard, P., Du, L., Zuo, F. et al.**, Genetic and immunologic evaluation of children with inborn errors of immunity and severe or critical COVID-19. *J. Allergy Clin. Immunol.* 2022. **150**: 1059–1073.

33 **Bodansky, A., Vazquez, S. E., Chou, J., Novak, T., Al-Musa, A., Young, C., Newhams, M. et al.**, NFKB2 haploinsufficiency identified via screening for IFNalpha2 autoantibodies in children and adolescents hospitalized with SARS-CoV-2-related complications. *J. Allergy Clin. Immunol.* 2022. **151**: 926–930

34 **Maccari, M. E., Scarselli, A., Di Cesare, S., Floris, M., Angius, A., Deodati, A., Chiriaco, M. et al.**, Severe toxoplasma gondii infection in a member of a NFKB2-deficient family with T and B cell dysfunction. *Clin. Immunol.* 2017. **183**: 273–277.

35 **Ramakrishnan, K. A., Rae, W., Barcenas-Morales, G., Gao, Y., Pengelly, R. J., Patel, S. V., Kumararatne, D. S. et al.**, Anticytokine autoantibodies in a patient with a heterozygous NFKB2 mutation. *J. Allergy Clin. Immunol.* 2018. **141**: 1479–1482 e1476.

36 **Sjogren, T., Bratland, E., Royrvik, E. C., Grytaas, M. A., Benneche, A., Knappskog, P. M., Kampe, O. et al.**, Screening patients with autoimmune endocrine disorders for cytokine autoantibodies reveals monogenic immune deficiencies. *J. Autoimmun.* 2022. **133**: 102917.

37 **Le Voyer, T., Gervais, A., Rosain, J., Audrey Parent, A. C., Darawan Rinchai, Lucy Bizien, Gonca Hancioglu et al.**, Impaired thymic AIRE expression underlies autoantibodies against type I IFNs in humans with inborn errors of the alternative NF-kB pathway. *Authorea* 2023. **133**: e166283

38 **Zhu, M., Chin, R. K., Christiansen, P. A., Lo, J. C., Liu, X., Ware, C., Siebenlist, U. et al.**, NF-kappaB2 is required for the establishment of central tolerance through an Aire-dependent pathway. *J. Clin. Invest.* 2006. **116**: 2964–2971.

39 **Cavadini, P., Vermi, W., Facchetti, F., Fontana, S., Nagafuchi, S., Mazzolari, E., Sediva, A. et al.**, AIRE deficiency in thymus of 2 patients with Omenn syndrome. *J. Clin. Invest.* 2005. **115**: 728–732.

40 **De Ravin, S. S., Cowen, E. W., Zarember, K. A., Whiting-Theobald, N. L., Kuhns, D. B., Sandler, N. G., Douek, D. C. et al.**, Hypomorphic Rag mutations can cause destructive midline granulomatous disease. *Blood* 2010. **116**: 1263–1271.

41 **Hetemaki, I., Kaustio, M., Kinnunen, M., Heikkila, N., Keskitalo, S., Nowlan, K., Miettinen, S. et al.**, Loss-of-function mutation in IKZF2 leads to immunodeficiency with dysregulated germinal center reactions and reduction of MAIT cells. *Sci. Immunol.* 2021. **6**: eabe3454.

42 **Weber, F., Cepok, S., Wolf, C., Berthele, A., Uhr, M., Bettecken, T., Buck, D. et al.**, Single-nucleotide polymorphisms in HLA- and non-HLA genes associated with the development of antibodies to interferon-beta therapy in multiple sclerosis patients. *Pharmacogenomics J.* 2012. **12**: 238–245.

43 **Andlauer, T. F. M., Link, J., Martin, D., Ryner, M., Hermanrud, C., Grummel, V., Auer, M. et al.**, Treatment- and population-specific genetic risk factors for anti-drug antibodies against interferon-beta: a GWAS. *BMC Med.* 2020. **18**: 298.

44 **Link, J., Lundkvist Ryner, M., Fink, K., Hermanrud, C., Lima, I., Brynedal, B., Kockum, I. et al.**, Human leukocyte antigen genes and interferon beta preparations influence risk of developing neutralizing anti-drug antibodies in multiple sclerosis. *PLoS One* 2014. **9**: e90479.

45 **Strobel, P., Murumagi, A., Klein, R., Luster, M., Lahti, M., Krohn, K., Schalke, B. et al.**, Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS-1). *J. Pathol.* 2007. **211**: 563–571.

46 **Liang, Z., Dong, X., Zhang, Z., Zhang, Q. and Zhao, Y.**, Age-related thymic involution: Mechanisms and functional impact. *Aging Cell* 2022. **21**: e13671.

47 **Toth, B., Wolff, A. S., Halasz, Z., Tar, A., Szuts, P., Ilyes, I., Erdos, M. et al.**, Novel sequence variation of AIRE and detection of interferon-omega antibodies in early infancy. *Clin. Endocrinol. (Oxf)* 2010. **72**: 641–647.

48 **Wolff, A. S., Sarkadi, A. K., Marodi, L., Karner, J., Orlova, E., Oftedal, B. E., Kisand, K. et al.**, Anti-cytokine autoantibodies preceding onset of autoimmune polyendocrine syndrome type I features in early childhood. *J. Clin. Immunol.* 2013. **33**: 1341–1348.

49 **Trown, P. W., Kramer, M. J., Dennin, R. A., Jr., Connell, E. V., Palleroni, A. V., Quesada, J. and Gutterman, J. U.**, Antibodies to human leucocyte interferons in cancer patients. *Lancet* 1983. **1**: 81–84.

50 **Gutterman, J. U., Fine, S., Quesada, J., Horning, S. J., Levine, J. F., Alexanian, R., Bernhardt, L. et al.**, Recombinant leukocyte A interferon: pharmacokinetics, single-dose tolerance, and biologic effects in cancer patients. *Ann. Intern. Med.* 1982. **96**: 549–556.

51 **Ronnblom, L. E., Janson, E. T., Perers, A., Oberg, K. E. and Alm, G. V.**, Characterization of anti-interferon-alpha antibodies appearing during recombinant interferon-alpha 2a treatment. *Clin. Exp. Immunol.* 1992. **89**: 330–335.

52 **Figlin, R. A., deKernion, J. B., Mukamel, E., Palleroni, A. V., Itri, L. M. and Sarna, G. P.**, Recombinant interferon alfa-2a in metastatic renal cell carcinoma: assessment of antitumor activity and anti-interferon antibody formation. *J. Clin. Oncol.* 1988. **6**: 1604–1610.

53 **Bell, J. B., Barfoot, R., Iveson, T., Powles, R. L. and Millar, B. C.**, Neutralising antibodies in patients with multiple myeloma receiving maintenance therapy with interferon alpha 2b. *Br. J. Cancer* 1994. **70**: 646–651.

54 **Stancek, D., Fuchsberger, N., Oltman, M., Schmeisser, H., Kontsek, P., Jahnova, E. and Hajnicka, V.**, Significance of anti-interferon-alpha2 and sICAM-1 activities in the sera of viral hepatitis B and C patients treated with human recombinant interferon-alpha2. *Acta. Virol.* 2001. **45**: 287–292.

55 **Hegen, H., Millonig, A., Bertolotto, A., Comabella, M., Giovanonni, G., Guger, M., Hoelzl, M. et al.**, Early detection of neutralizing antibodies to

interferon-beta in multiple sclerosis patients: binding antibodies predict neutralizing antibody development. *Mult. Scler.* 2014. **20**: 577–587.

56 **Sorensen, P. S., Koch-Henriksen, N., Ross, C., Clemmesen, K. M. and Bendtzen, K.**, Danish Multiple Sclerosis Study Group, Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. *Neurology* 2005. **65**: 33–39.

57 **Ikeda, Y., Toda, G., Hashimoto, N., Umeda, N., Miyake, K., Yamanaka, M. and Kurokowa, K.**, Naturally occurring anti-interferon-alpha 2a antibodies in patients with acute viral hepatitis. *Clin. Exp. Immunol.* 1991. **85**: 80–84.

58 **Fall, L. S., Chams, V., Le Coq, H., Fouchard, M., M'Bika, J. P., Gringeri, A., Santagostino, E. et al.**, Evidence for an antiviral effect and interferon neutralizing capacity in human sera; variability and implications for HIV infection. *Cell. Mol. Biol. (Noisy-le-grand)* 1995. **41**: 409–416.

59 **Shaw, E. R., Rosen, L. B., Cheng, A., Dobbs, K., Delmonte, O. M., Ferre, E. M. N., Schmitt, M. M. et al.**, Temporal dynamics of anti-type 1 interferon autoantibodies in patients with coronavirus disease 2019. *Clin. Infect. Dis.* 2022. **75**: e1192–e1194.

60 **Chang, S. E., Feng, A., Meng, W., Apostolidis, S. A., Mack, E., Artandi, M., Barman, L. et al.**, New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat. Commun.* 2021. **12**: 5417.

61 **Feng, A., Yang, E., Moore, A., Dhingra, S., Chang, S., Yin, X., Pi, R. et al.**, Autoantibodies are highly prevalent in non–SARS-CoV-2 respiratory infections and critical illness. *JCI Insight* 2023. **8**: e163150

62 **Steels, S., Van Elslande, J., Leuven, C.-S. G., De Munter, P. and Bossuyt, X.**, Transient increase of pre-existing anti-IFN-alpha2 antibodies induced by SARS-CoV-2 infection. *J. Clin. Immunol.* 2022. **42**: 742–745.

63 **Scordio, M., Frasca, F., Santinelli, L., Sorrentino, L., Pierangeli, A., Turriziani, O., Mastroianni, C. M. et al.**, High frequency of neutralizing antibodies to type I Interferon in HIV-1 patients hospitalized for COVID-19. *Clin. Immunol.* 2022. **241**: 109068.

64 **Ning, W., Xu, W., Cong, X., Fan, H., Gilkeson, G., Wu, X., Hughes, H. et al.**, COVID-19 mRNA vaccine BNT162b2 induces autoantibodies against type I interferons in a healthy woman. *J. Autoimmun.* 2022. **132**: 102896.

65 **Burbelo, P. D., Seam, N., Groot, S., Ching, K. H., Han, B. L., Meduri, G. U., Iadarola, M. J. et al.**, Rapid induction of autoantibodies during ARDS and septic shock. *J. Transl. Med.* 2010. **8**: 97.

66 **Wang, E. Y., Mao, T., Klein, J., Dai, Y., Huck, J. D., Jaycox, J. R., Liu, F. et al.**, Diverse functional autoantibodies in patients with COVID-19. *Nature* 2021. **595**: 283–288.

67 **Asgari, N., Kyvik, K. O., Steenstrup, T., Stenager, E. and Lillevang, S. T.**, Antibodies against interferon-beta in neuromyelitis optica patients. *J. Neurol. Sci.* 2014. **339**: 52–56.

68 **Metcalf, T. U., Cubas, R. A., Ghneim, K., Cartwright, M. J., Grevenynghe, J. V., Richner, J. M., Olagnier, D. P. et al.**, Global analyses revealed age-related alterations in innate immune responses after stimulation of pathogen recognition receptors. *Aging Cell* 2015. **14**: 421–432.

69 **Cleveland, M. G., Lane, R. G. and Klimpel, G. R.**, Enhanced interferon-alpha/beta (IFN-alpha/beta) and defective IFN-gamma production in chronic graft versus host disease: a potential mechanism for immunosuppression. *Cell. Immunol.* 1987. **110**: 120–130.

70 **Nestle, F. O., Conrad, C., Tun-Kyi, A., Homey, B., Gombert, M., Boyman, O., Burg, G. et al.**, Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. *J. Exp. Med.* 2005. **202**: 135–143.

71 **Gul, E., Sayar, E. H., Gungor, B., Eroglu, F. K., Surucu, N., Keles, S., Guner, S. N. et al.**, Type I IFN-related NETosis in ataxia telangiectasia and Artemis deficiency. *J. Allergy Clin. Immunol.* 2018. **142**: 246–257.

72 **Su, L. and David, M.**, Inhibition of B cell receptor-mediated apoptosis by IFN. *J. Immunol.* 1999. **162**: 6317–6321.

73 **Keller, E. J., Patel, N. B., Patt, M., Nguyen, J. K. and Jorgensen, T. N.**, Partial protection from lupus-like disease by B-cell specific type I interferon receptor deficiency. *Front. Immunol.* 2020. **11**: 616064.

74 **De Maeyer-Guignard, J. and De Maeyer, E.**, Natural antibodies to interferon-alpha and interferon-beta are a common feature of inbred mouse strains. *J. Immunol.* 1986. **136**: 1708–1711.

75 **De Maeyer-Guignard, J., Cachard-Thomas, A. and De Maeyer, E.**, Naturally occurring anti-interferon antibodies in Lou/c rats. *J. Immunol.* 1984. **133**: 775–778.

76 **Pozzetto, B., Mogensen, K. E., Tovey, M. G. and Gresser, I.**, Characteristics of autoantibodies to human interferon in a patient with varicella-zoster disease. *J. Infect. Dis.* 1984. **150**: 707–713.

77 **Bayat, A., Burbelo, P. D., Browne, S. K., Quinlivan, M., Martinez, B., Holland, S. M., Buvanendran, A. et al.**, Anti-cytokine autoantibodies in postherpetic neuralgia. *J. Transl. Med.* 2015. **13**: 333.

78 **Troya, J., Bastard, P., Planas-Serra, L., Ryan, P., Ruiz, M., de Carranza, M., Torres, J. et al.**, Neutralizing autoantibodies to type I IFNs in >10% of patients with severe COVID-19 pneumonia hospitalized in Madrid, Spain. *J. Clin. Immunol.* 2021. **41**: 914–922.

79 **Goncalves, D., Mezidi, M., Bastard, P., Perret, M., Saker, K., Fabien, N., Pescarmona, R. et al.**, Antibodies against type I interferon: detection and association with severe clinical outcome in COVID-19 patients. *Clin. Transl. Immunology* 2021. **10**: e1327.

80 **Solanich, X., Rigo-Bonnin, R., Gumucio, V. D., Bastard, P., Rosain, J., Philippot, Q., Perez-Fernandez, X. L. et al.**, Pre-existing autoantibodies neutralizing high concentrations of type I interferons in almost 10% of COVID-19 patients admitted to intensive care in Barcelona. *J. Clin. Immunol.* 2021. **41**: 1733–1744.

81 **Chauvineau-Grenier, A., Bastard, P., Servajean, A., Gervais, A., Rosain, J., Jouanguy, E., Cobat, A. et al.**, Autoantibodies neutralizing type I interferons in 20% of COVID-19 deaths in a French Hospital. *J. Clin. Immunol.* 2022. **42**: 459–470.

82 **Frasca, F., Scordio, M., Santinelli, L., Gabriele, L., Gandini, O., Criniti, A., Pierangeli, A. et al.**, Anti-IFN-alpha/-omega neutralizing antibodies from COVID-19 patients correlate with downregulation of IFN response and laboratory biomarkers of disease severity. *Eur. J. Immunol.* 2022. **52**: 1120–1128.

83 **Busnadiego, I., Abela, I. A., Frey, P. M., Hofmaenner, D. A., Scheier, T. C., Schuepbach, R. A., Buehler, P. K. et al.**, Critically ill COVID-19 patients with neutralizing autoantibodies against type I interferons have increased risk of herpesvirus disease. *PLoS Biol.* 2022. **20**: e3001709.

84 **Akbil, B., Meyer, T., Stubbemann, P., Thibeault, C., Staudacher, O., Niemeyer, D., Jansen, J. et al.**, Early and rapid identification of COVID-19 patients with neutralizing type I interferon auto-antibodies. *J. Clin. Immunol.* 2022. **42**: 1111–1129.

85 **Credle, J. J., Gunn, J., Sangkhapreecha, P., Monaco, D. R., Zheng, X. A., Tsai, H. J., Wilbon, A. et al.**, Unbiased discovery of autoantibodies associated with severe COVID-19 via genome-scale self-assembled DNA-barcoded protein libraries. *Nat. Biomed. Eng.* 2022. **6**: 992–1003.

86 **Eto, S., Nukui, Y., Tsumura, M., Nakagama, Y., Kashimada, K., Mizoguchi, Y., Utsumi, T. et al.**, Neutralizing type I interferon autoantibodies in Japanese patients with severe COVID-19. *J. Clin. Immunol.* 2022. **42**: 1360–1370.

87 **Zhang, Q., Pizzorno, A., Miorin, L., Bastard, P., Gervais, A., Le Voyer, T., Bizien, L. et al.**, Effort, C. H. G., Etablissement Francais du Sang Study Group, Constances, C., Study, C. D., Cerba HealthCare, G., Lyon Antigrippe Working, G., Group, R. I. W., Autoantibodies against type I IFNs in patients with critical influenza pneumonia. *J. Exp. Med.* 2022. 219.

88 **Manry, J., Bastard, P., Gervais, A., Le Voyer, T., Rosain, J., Philippot, Q., Michailidis, E. et al.**, The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies. *Proc. Natl. Acad. Sci. U. S. A.* 2022. **119**: e2200413119.

89 **Bastard, P., Michailidis, E., Hoffmann, H. H., Chbihi, M., Le Voyer, T., Rosain, J., Philippot, Q. et al.**, Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. *J. Exp. Med.* 2021. 218.

90 **Prummer, O., Frickhofen, N., Digel, W., Heimpel, H. and Porzsolt, F.**, Spontaneous interferon-alpha antibodies in a patient with pure red cell aplasia and recurrent cutaneous carcinomas. *Ann. Hematol.* 1991. **62**: 76–80.

91 **Hetemaki, I., Laakso, S., Valimaa, H., Kleino, I., Kekalainen, E., Makitie, O. and Arstila, T. P.**, Patients with autoimmune polyendocrine syndrome type 1 have an increased susceptibility to severe herpesvirus infections. *Clin. Immunol.* 2021. **231**: 108851.

92 **Meisel, C., Akbil, B., Meyer, T., Lankes, E., Corman, V. M., Staudacher, O., Unterwalder, N. et al.**, Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1. *J. Clin. Invest.* 2021. 131.

93 **Lemarquis, A., Campbell, T., Aranda-Guillen, M., Hennings, V., Brodin, P., Kampe, O., Blennow, K. et al.**, Severe COVID-19 in an APS1 patient with interferon autoantibodies treated with plasmapheresis. *J. Allergy Clin. Immunol.* 2021. **148**: 96–98.

94 **Bastard, P., Orlova, E., Sozaeva, L., Levy, R., James, A., Schmitt, M. M., Ochoa, S. et al.**, Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J. Exp. Med.* 2021. 218.

95 **Abers, M. S., Rosen, L. B., Delmonte, O. M., Shaw, E., Bastard, P., Imberti, L., Quaresima, V. et al.**, Neutralizing type-I interferon autoantibodies are associated with delayed viral clearance and intensive care unit admission in patients with COVID-19. *Immunol. Cell Biol.* 2021. **99**: 917–921.

96 **Koning, R., Bastard, P., Casanova, J. L., Brouwer, M. C. and van de Beek, D.**, with the Amsterdam, U. M. C. C.-B. I., Autoantibodies against type I interferons are associated with multi-organ failure in COVID-19 patients. *Intensive Care Med.* 2021. **47**: 704–706.

97 **Lopez, J., Mommert, M., Mouton, W., Pizzorno, A., Brengel-Pesce, K., Mezidi, M., Villard, M. et al.**, Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. *J. Exp. Med.* 2021. 218.

98 **van der Wijst, M. G. P., Vazquez, S. E., Hartoularos, G. C., Bastard, P., Grant, T., Bueno, R., Lee, D. S. et al.**, Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. *Sci. Transl. Med.* 2021. **13**: eabh2624.

99 **Kisand, K., Link, M., Wolff, A. S., Meager, A., Tserel, L., Org, T., Murumagi, A. et al.**, Interferon autoantibodies associated with AIRE deficiency decrease the expression of IFN-stimulated genes. *Blood* 2008. **112**: 2657–2666.

100 **Lin, C. H., Chi, C. Y., Shih, H. P., Ding, J. Y., Lo, C. C., Wang, S. Y., Kuo, C. Y. et al.**, Identification of a major epitope by anti-interferon-gamma autoantibodies in patients with mycobacterial disease. *Nat. Med.* 2016. **22**: 994–1001.

101 **Sokal, A., Bastard, P., Chappert, P., Barba-Spaeth, G., Fourati, S., Vanderberghe, A., Lagouge-Roussey, P. et al.**, Human type I IFN deficiency does not impair B cell response to SARS-CoV-2 mRNA vaccination. *J. Exp. Med.* 2023. 220.

102 **Bastard, P., Vazquez, S., Liu, J., Laurie, M. T., Wang, C. Y., Gervais, A., Le Voyer, T. et al.**, Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs. *Sci. Immunol.* 2022. eabp8966.

103 **de Prost, N., Bastard, P., Arrestier, R., Fourati, S., Mahevas, M., Burrel, S., Dorgham, K. et al.**, Plasma exchange to rescue patients with autoantibodies against type I interferons and life-threatening COVID-19 pneumonia. *J. Clin. Immunol.* 2021. **41**: 536–544.

104 **Lee, D. S. W., Rojas, O. L. and Gommerman, J. L.**, B cell depletion therapies in autoimmune disease: advances and mechanistic insights. *Nat. Rev. Drug. Discov.* 2021. **20**: 179–199.

105 **Bastard, P., Levy, R., Henriquez, S., Bodemer, C., Szwebel, T. A. and Casanova, J. L.**, Interferon-beta therapy in a patient with incontinentia pigmenti and autoantibodies against type I IFNs infected with SARS-CoV-2. *J. Clin. Immunol.* 2021. **41**: 931–933.

106 **Reis, G., Silva E. A. S. M., Silva D. C. M., Thabane, L., Campos, V. H. S., Ferreira, T. S., Santos, C. V. Q. et al.**, Early treatment with pegylated interferon lambda for Covid-19. *N. Engl. J. Med.* 2023. **388**: 518–528.

Abbreviations: **APS-1**: autoimmune polyendocrinopathy syndrome type 1 · **ARDS**: acute respiratory distress syndrome · **autoAbs**: autoantibodies · **CID-G/AI**: combined immunodeficiency with granulomatous disease and/or autoimmunity · **CMV**: cytomegalovirus · **HSV**: herpes simplex virus · **IFN-I**: type I IFN · **ISG**: IFN-stimulated gene · **SLE**: systemic lupus erythematosus · **SS**: Sjögren's syndrome · **VZV**: varicella-zoster virus

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