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Current Opinion in Immunology

Monogenic autoimmunity and infectious diseases: the double-edged sword of immune dysregulation

Tarin M Bigley and Megan A Cooper

The study of monogenic autoimmune diseases has provided key insights into molecular mechanisms involved in development of autoimmunity and immune tolerance. It has also become clear that such inborn errors of immunity (IEIs) frequently present clinically not only with autoimmune diseases, but also frequently have increased susceptibility to infection. The genes associated with monogenic autoimmunity influence diverse functional pathways, and the resulting immune dysregulation also impacts the complex and coordinated immune response to pathogens, for example type I interferon and cytokine signaling, the complement pathway and proper differentiation of the immune response. The SARS-CoV-2 pandemic has highlighted how monogenic autoimmunity can increase risk for serious infection with the discovery of severe disease in patients with pre-existing antibodies to Type I IFNs. This review discusses recent insight into the relationship between monogenic autoimmunity and infectious diseases.

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Introduction

The increased availability and utilization of high-throughput DNA sequencing has brought about a rapid increase in the identification of genes associated with monogenic autoimmunity, which are classified as inborn errors of immunity (IEI) by the International Union of Immunological Sciences Expert Committee [1]. Indeed, the transition in terminology from 'primary immunodeficiency' to 'IEI' reflects the understanding that these diseases are more complex than simply susceptibility to infection. Immune dysregulation with autoimmunity, autoinflammation, cancer susceptibility, and bone marrow failure can all be clinical features of IEIs. Identification of specific genes associated with monogenic autoimmunity and observation of the clinical consequences have accelerated our understanding of the balance between control of infections and autoimmunity [2].

Autoimmune diseases are characterized by abnormal activation of the innate and adaptive immune system leading to self-reactive T and B cells and development of autoantibodies, which lead to inflammation and tissue damage. The genetic risk factors associated with many monogenic autoimmune diseases can also result in increased risk of infection, although there is significant clinical diversity with regards to autoimmune manifestations and pathogen susceptibility [2]. This highlights the diverse pathways that are important for control of both immunologic tolerance and pathogen defense. In this review we discuss recent discoveries in monogenic autoimmunity, highlighting examples of defects in genes involved in T cell tolerance, the complement pathways, interferon signaling, and STAT signaling and their contribution to autoimmunity and pathogen susceptibility (Figure 1), including recent evidence for susceptibility to SARS-CoV-2 associated with monogenic autoimmunity.

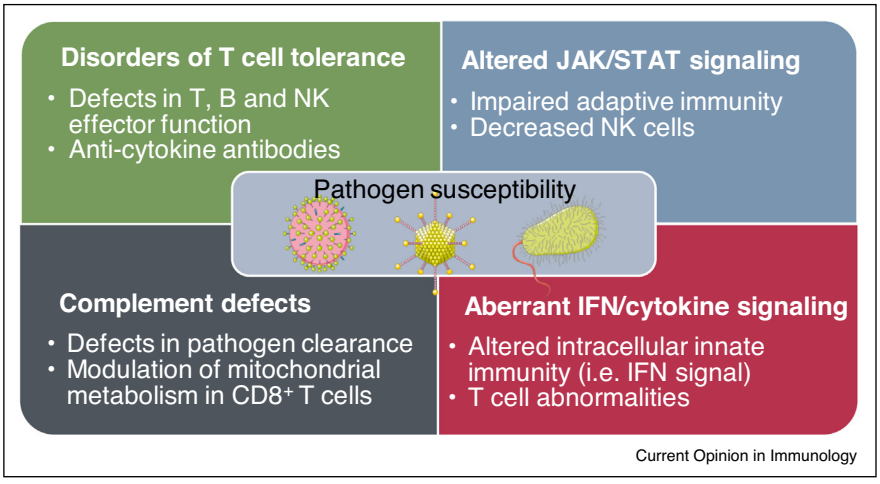
Monogenic autoimmunity and susceptibility to infection

Genes associated with monogenic autoimmunity are involved in diverse immunologic processes. Defects in genes involved in monogenic autoimmunity result in specific patterns of autoimmunity based on their role in different aspects of the immune system. While many patients with monogenic autoimmunity may be at increased risk for infection due to immunomodulatory treatment, we highlight recent discoveries that provide mechanistic insight into how genes involved in monogenic autoimmunity also contribute to increased susceptibility to infection (Figure 1).

Disorders of T cell tolerance

Both central and peripheral mechanisms of T cell tolerance are important for control of self-reactive T cell responses and autoimmunity. Autoimmune endocrinopathies are a common pattern of autoimmunity in disorders of T cell tolerance [1]. Central tolerance of developing T cells occurs in the thymus when thymocytes interact with thymic antigen presenting cells (eg. medullary thymic epithelial cells and thymic dendritic cells) that present a wide array of antigens expressed through the body, known as tissue-restricted antigens (TRAs) [3]. The

Figure 1



Mechanisms of pathogen susceptibility in different groups of monogenic autoimmune disorders highlighted here.

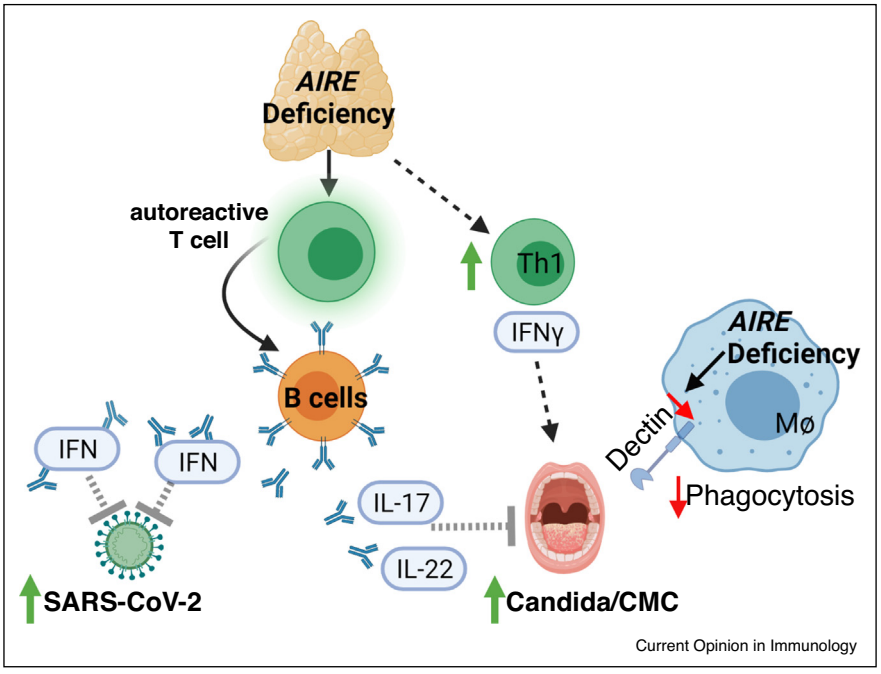
autoimmune regulator (AIRE) transcription factor stimulates expression of TRAs [3]. Deficiency of *AIRE* is associated with monogenic autoimmunity, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyendocrine syndrome type 1 (APS-1), due to defects in negative selection of T cells. In addition to autoimmunity due to defects in T cell tolerance, patients with *AIRE* deficiency suffer from chronic mucocutaneous candidiasis (CMC). In humans, susceptibility to CMC is associated with impaired Th17 immunity, as demonstrated by patients with monogenic defects in IL17F and IL17RA/C and in IEI with impaired Th17 immunity (e.g. STAT1 GOF) [4]. Patients with AIRE deficiency have a high rate of anti-cytokine autoantibodies, including anti-IL-17A, IL17F, and IL22, thought to be due to autoreactive T cell stimulation of B cells [5,6]. These Th17-associated cytokines autoantibodies are associated with susceptibility to CMC in APECED patients, providing a mechanistic link between T cell selection and infectious susceptibility (Figure 2). A recent study in *Aire* deficient mice suggested that there was an increased Th1 response to *Candida* infection, with similar responses seen in oral mucosa from APECED patients [7•]. In this mouse model, CMC was dependent on T cells and IFNγ, suggesting an additional mechanism that may contribute to CMC susceptibility. There may also be non-T cell effects of AIRE, with a direct role for AIRE in pathogen response proposed through effects on Dectin-1 and Dectin-2 in macrophages, which are important receptors for recognition and phagocytosis of *Candida* (Figure 2) [8].

Peripheral tolerance occurs when autoreactive T and B cells escape central tolerance but are inhibited from inducing harm through tolerance checkpoints such as quiescence, ignorance, anergy, exhaustion, senescence and death (reviewed in detail in Ref. [9]). Several disorders of peripheral tolerance have demonstrated overlap with requirements for pathogen defense. Deficiencies in the CTLA-4 pathway, including regulators of CTLA-4 trafficking, LRBA and DEF6, are associated with autoimmune disease due to defects in T cell tolerance resulting from loss of inhibitory signaling [10]. They are also associated with recurrent bacterial and fungal infections, and increased susceptibility to herpesvirus infections [10–12]. The mechanism for this infectious susceptibility is yet unknown. Patients with CTLA-4 deficiency have decreased $CD8^+$ T cells and potentially a trend toward increased expression of the senescence marker, CD57 on $CD8^+$ T cells [13,14]. Interestingly, CTLA-4 was shown to be expressed on activated NK cells, with NK cells from CTLA-4 haploinsufficiency patients showing decreased effector function [15].

IL-2 is an important cytokine for regulatory T cell (Treg) development and effector T cell proliferation, and deficiency of IL-2Rα (CD25) results in autoimmune polyendocrinopathy and increased susceptibility to bacterial infections and CMV [16]. IL-2 signaling through IL-2Rβ is known to be important for $CD8^+$ T cell cytotoxic function and Treg proliferation in mice [17]. Defects in IL-2Rβ had not been observed in humans until two separate groups recently reported human IL-2Rβ deficiency resulting in autoimmunity, atopy and increased EBV and CMV disease in humans [18•,19•]. These studies demonstrate the pleiotropic effects of IL-2 on T cell tolerance and effector function.

Finally, ITCH is a U3 ubiquitin ligase that suppresses inflammation and promotes tolerance through its impact on T cells, especially Th2 cells and Tregs (through enhancement of the *FOXP3* transcription factor), and B

Figure 2



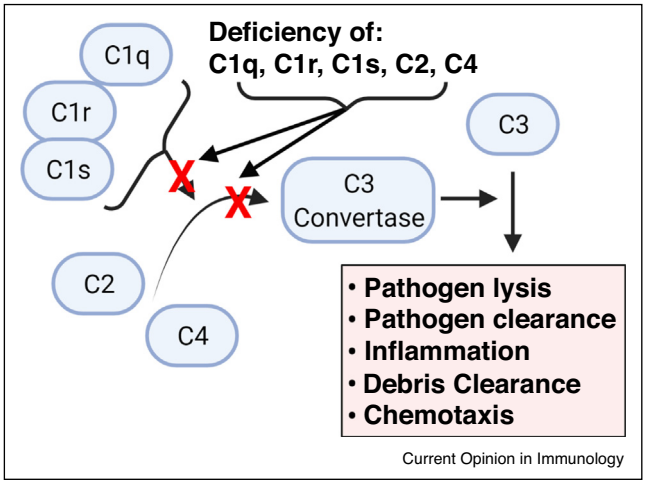
Mechanisms of *AIRE* deficiency-associated pathogen susceptibility.
AIRE deficiency in the thymus results in altered T cell selection and autoreactive antibodies, including anti-IL-17 antibodies, which are associated with susceptibility to chronic mucocutaneous candidiasis (CMC), and anti-Type I IFN antibodies, which increase disease severity with SARS-CoV-2 infection. Studies in an animal model suggests that a dysregulated Th1 response in the mucosa may also be associated with CMC. *AIRE* deficiency in macrophages (Mø) decreases Dectin-1 and Dectin-2 expression, and may also contribute to defects in phagocytosis of *Candida* and CMC.

cells [20,21]. Autoimmunity associated with a nonsense variant in *ITCH* in a patient was first reported in 2010 [22]. In 2019, two groups reported cases of polyautoimmunity, including autoimmune endocrinopathies, and recurrent respiratory tract infection associated with *ITCH* variants [23,24]. Interestingly, ITCH was shown to be important in the antibody response to viral infection in mice, suggesting a potential mechanism for increased infection in ITCH deficiency [25].

Complement deficiencies

The complement cascade is an important part of the innate immune system, contributing to opsonization, clearance of microbes and cellular debris, and promoting inflammation [26]. Deficiency in early complement proteins is now well-described to be associated with monogenic autoimmunity, and this has been suggested to be due to increased inflammation related to poor pathogen clearance and defective clearance of autoantigens after apoptosis and tissue damage. Deficiencies in C1q, C2 and C4, but not C3, can present with systemic lupus erythematosus (SLE)-like disease and/or recurrent bacterial infections (Figure 3) [1,26]. A recent study in C1q

Figure 3



Defects in early complement components result in pathogen susceptibility.
Deficiency of early complement components result in impaired formation of the C3 convertase that is required for complement-mediated response to pathogens that can also contribute to inflammation in autoimmunity.

deficient mice showed that C1q can regulate the response of $CD8^+$ T cells to autoantigens and LCMV infection through modulation of mitochondrial metabolism, establishing a non-complement pathway mediated mechanism for immunodeficiency [27•]. C1q may also inhibit type I interferons (IFN) and other cytokines through interaction with Ig-like receptor (LAI) 1 on dendritic cells, inhibiting TLR7 and TLR9-mediated IFNα, IL-6, IL-8 and TNFα expression [28]. The impact of C1q, as well as C1r, on IFN signaling is supported by high type I IFN scores reported in a patient with C1q deficiency-associated SLE [29]. Together, these studies underscore the relevance of the non-canonical complement pathway alterations in autoimmunity and infection.

Autoimmunity resulting from aberrant interferon and cytokine signaling

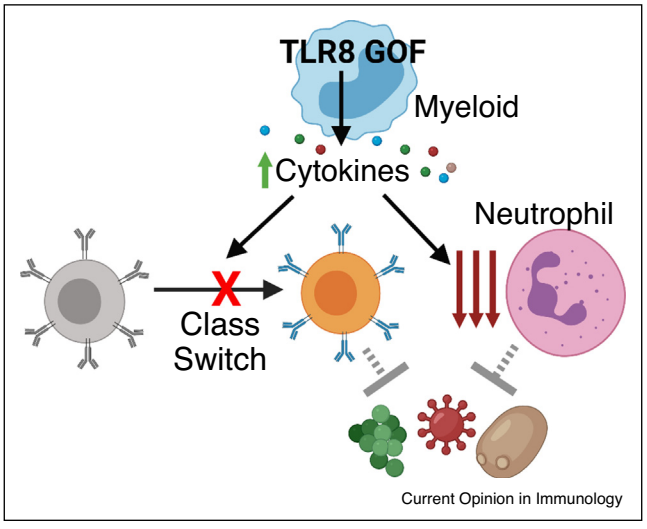
Type I IFN signaling is stimulated in response to pathogens and mediates important pathogen responses. Increased type I IFN signaling is observed in polygenic autoimmune disease such as SLE, as well as monogenic disorders of the type I IFN pathway, called interferonopathies [30]. Interferonopathies are typically associated with autoinflammatory manifestations rather than autoimmune disease, however autoimmune features are observed in some interferonopathies as is the case for *IFIH1* and *TREX1* which are associated with Aicardi-Goutières syndrome and lupus-like disease [1]. Several recent studies have evaluated how type I IFN signaling is dysregulated in specific monogenic autoimmune diseases and given insight into susceptibility to infection.

COPA syndrome is an autoimmune disease characterized by pulmonary hemorrhage, interstitial lung disease, arthritis, nephritis and autoantibodies caused by dominant variants in the *COPA* gene, the product of which is involved in transport of vesicle between with ER and Golgi [31]. Increased susceptibility to infection is not typically described, although a case series reported several patients who presented with multiple infections including acute pyelonephritis, meningitis and recurrent respiratory infections [32]. Recent studies have clarified that a key feature of this disorder is increased type I IFN signaling due to inability of mutant COPA protein to transport active STING from the Golgi to the endoplasmic reticulum [33••,34•,35]. Deng *et al.* showed that $Copa^{E241K/+}$ knock-in mice develop autoreactive T cells, decreased Tregs in the periphery, and autoimmune disease [36•]. Moreover, negative thymic selection of autoreactive thymocytes by thymic epithelial cells was impaired.

STIM1 deficiency manifests as recurrent bacterial infections, autoimmune hemolytic anemia, nephrotic syndrome, as well as dysmorphic features [37]. STIM1 is a calcium channel that was recently shown to influence Th17 cell metabolism, which is important for antifungal immunity [38]. Interestingly, similar to COPA, STIM1 deficiency resulted in increased type I IFN response, which was suggested to be due to loss of STIM1-mediated retention of STING in the ER [39••]. How defects in COPA and STIM1 that result in increased type I IFN signaling impact susceptibility to infection is unclear, but a mouse model of STING gain-of-function suggests that constitutive activation of STING may increase susceptibility to infection with a herpesvirus [40]. Additional studies of patient samples and *in vivo* models of COPA syndrome and STIM1 deficiency will increase our understanding of how dysregulated IFN responses influence susceptibility and response to infections.

Toll-like receptor 8 (TLR8) is an endosomal sensor of single stranded RNA [41]. We recently described an IEI due to monogenic mosaic and germline variants in TLR8 associated with immune dysregulation, susceptibility to infection and bone marrow failure. Patients had elevated serum cytokines, including IFN-γ and others such as IL-18 and IL12/23 p40, although interestingly these patients do not have a strong Type I IFN signature [42]. Patients with TLR8 GOF have neutropenia, and immune phenotyping demonstrated highly activated peripheral blood T cells and defects in class-switched B cells. Differentiation of macrophages from patient-derived induced pluripotent stem cells showed increased cytokine responses to TLR8 ligand stimulation. Patients with TLR8 GOF have infections related to these immunologic defects (Figure 4). While the mechanism of this immune suppression is uncertain, the phenotype in mosaic patients suggests a dominant and non-intrinsic effect of cytokines

Figure 4



Mechanisms of pathogen susceptibility in TLR8 GOF.
TLR8 is expressed primarily in myeloid cells. Patients with TLR8 GOF have increased serum cytokines and production of pro-inflammatory cytokines in patient-derived macrophages. This cytokine expression is hypothesized to lead to impaired class switching of B cells and severe neutropenia, with resulting infectious susceptibility.

Table 1

Monogenic autoimmune disease with aberrant JAK/STAT signaling

Disease	Gene	Inheritance	Molecular effects	Immunologic defects	Autoimmunity	Pathogen susceptibility
JAK1 GOF [62]	*JAK1*	AD (GOF)	Increased STAT1 phosphorylation as baseline, increased STAT3 phosphorylation after IL-6 stimulation	Eosinophilia with normal IgE, atopy	AITD	Recurrent viral infections
SOCS1 haplo-insufficiency [52•,53•,54•]	*SOCS1*	AD (LOF)	Increased STAT1 and STAT5 phosphorylation after IFNγ, IL-2, and IL-4 stimulation	Lymphoproliferation in some patients. Decreased Treg numbers. Low switched memory B cells	Autoimmune cytopenias, psoriasis, SLE, polyarthritis, spondyloarthritis, celiac disease, AITD, AIH, autoimmune pancreatitis	Respiratory infections
STAT1 deficiency [1,63]	*STAT1*	AD or AR (LOF)	Deficient STAT1 signaling including IFN responses	Impaired Th1 and Th17 immunity	AITD, autoimmune cytopenias, celiac disease	CMC, recurrent bacterial infections (mycobacterium), herpes and fungal infections
STAT1 GOF [43–45]	*STAT1*	AD (GOF)	STAT1 hyperphosphorylation and transcriptional activity and impaired STAT3 activation	Impaired Th17 and IL-22 immunity. Decreased *Candida*-specific Th17 and Th22 response. Rarely B cell lymphopenia and hypogammaglobulinemia.	AITD, T1DM, autoimmune cytopenias, psoriasis, SLE, scleroderma, AIH, IBD, celiac disease	Increased bacteria and herpes infections, *Cryptococcus* infections, CMC
STAT2 GOF [64]	*STAT2*	AR (GOF)	Abrogated ubiquitin-specific protease 18 (USP18) interaction resulting in elevated type I IFN signaling and prolong JAK-STAT signaling.	Decreased NK and $CD8^+$ T cell granule release. T cell lymphopenia and hypogammaglobulinemia in one patient.	Autoinflammatory: fever, cytopenias, nephropathy, hepatosplenomegaly, elevated liver enzymes, thrombotic microangiopathy, seizures, intracerebral hemorrhage.	None reported
STAT3 GOF [46,47]	*STAT3*	AD (GOF)	Increased STAT3 transcriptional activity with stimulation, possibly decreased STAT1 and STAT5 phosphorylation.	Reduced T and B cell numbers, hypogammaglobulinemia, decreased peripheral Treg numbers, in some patients increased Th17 cells	Enteropathy, autoimmune cytopenias, ILD, T1DM, AITD, arthritis, AIH, scleroderma	Varied including viral respiratory tract infections, herpesvirus infections, bacterial infections
STAT5b deficiency [65]	*STAT5B*	AR	Defects in STAT5b signaling and target genes including immune pathways and IGF1	Reduced Treg number/function, high IgG and IgE, reduced γδ−T and NK cells	AITD, autoantibodies, arthritis, ITP lymphocytic interstitial pneumonitis	Viral respiratory tract infections, Pneumocystis jirovecii pneumonia, severe herpesvirus infections
TOM1 LOF [50]	*TOM1*	AD	Impaired TOM1-TOLLIP interaction resulting in decreased STAT1, STAT3, and STAT5 phosphorylation.	Low memory and class switch B cells, hypo-gammaglobulinemia. Impaired Th1 and Th17 differentiation. Deceased T effector memory.	Oligoarthritis, psoriasis, autoimmune enteropathy, ILD	Recurrent respiratory infections, EBV viremia

Abbreviations: ADautosomal dominant; AIHautoimmune hepatitis; AIHAautoimmune hemolytic anemia; AITDautoimmune thyroid disease; ARautosomal recessive; GOFgain of function; ITPimmune thrombocytopenic purpura; JIAjuvenile idiopathic arthritis; LOFloss of function; CMCchronic mucocutaneous candidiasis; SLEsystemic lupus erythematosus; T1DMtype 1 diabetes mellitus.

in these patients, potentially within the bone marrow microenvironment.

STAT signaling

The JAK/STAT pathway plays an important role in transducing signals from extracellular cytokines to intracellular signaling pathways that mediate a variety of responses. Alterations in JAK/STAT signaling are now well-described in monogenic autoimmunity including STAT1, STAT3, and STAT5b, with prominent T cell dysregulation, infectious susceptibility, and an autoimmune pattern including cytopenias, thyroid disease, and gastrointestinal disease being common features (Table 1). Gain-of-function (GOF) *STAT1* variants result in impairment of IL-17 and IL-22 mediated immunity and abnormal B cell differentiation, contributing to humoral defects and increased risk of candidiasis [43–45]. Patients with STAT3 GOF have early onset autoimmunity, but also susceptibility to infection associated with antibody deficiency [46,47].

TOM1 (target of Myb protein 1) is a lysosomal adapter protein thought to be involved maturation of the autophagosome and trafficking of endosomal cargo [48,49]. A newly described pathogenic variant in *TOM1* (G307D) presented clinically as oligoarthritis, psoriasis, autoimmune enteropathy, interstitial lung disease, hypogammaglobulinemia, recurrent URIs, and EBV viremia [50]. This variant was associated with decreased STAT1, 3 and 5 signaling, poor Th1 and Th17 differentiation, low class switch memory B cells, as well as decreased NK cell numbers. This was attributed to impaired TOM1 interaction with TOLLIP. The mechanism resulting in altered STAT signaling in TOM1-associated disease is yet unknown, although TOLLIP deficiency has been demonstrated to decrease STAT5 expression, perhaps through its function in autophagy [51]

Another recent example of altered STAT signaling associated with autoimmunity and infections is that of haploinsufficiency of suppressor of cytokine signaling-1 (SOCS1). SOCS1 attenuates signaling of multiple STATs (particularly STAT1) and is upregulated as a compensatory response to JAK/STAT signaling. These patients have early onset autoimmunity including cytopenias and even systemic lupus erythematosus, highlighting the importance of tight regulation of this system in human immunity [52•,53•,54•]. Together, these studies demonstrate the relationship between autoimmunity and pathogen susceptibility in dysregulated STAT and cytokine signaling.

Lessons learned from SARS-CoV-2

The SARS-CoV-2 pandemic has provided insight into the variability of the immune response to a pathogen infecting a heterogenous and immunologically naïve population. Type I IFN signaling has emerged as a critical requirement for an effective immune response to acute SARS-CoV2 infection. In addition, immune dysregulation has clearly been induced in some COVID-19 patients as seen in multisystem inflammatory syndrome in children (MIS-C), with the characteristic features and clinical course suggestive of an underlying immunologic defect in these previously healthy children brought out by this unique virus [55,56].

Genomic sequencing of a cohort of 650 individuals with severe acute COVID-19 identified 3.5% of patients with monogenic defects in the type I IFN signaling pathway [57]. Functional studies proving pathogenicity of both known and novel defects demonstrated the importance of this pathway for efficient control of SARS-CoV2. In a complementary study of almost 1000 patients without genetic defects in the type I IFN pathway, neutralizing autoantibodies against type I IFNs were associated with severe COVID-19, illustrating a mechanism by which loss of tolerance can directly lead to infection susceptibility [58]. Patients with *AIRE* deficiency and APECED/APS-I almost uniformly develop neutralizing type I IFN autoantibodies, which previously were not recognized to be associated with infectious susceptibility [59]. The Casanova and Lionakis laboratories recently demonstrated that in contrast to most other patients with IEIs, patients with *AIRE* deficiency and COVID-19 develop severe pneumonia and suffer from high mortality associated with these pre-existing auto-antibodies (Figure 2) [60••]. This finding provides a direct link between monogenic autoimmunity, autoantibodies, and infectious susceptibility. While in MIS-C, there has not yet been a report of a monogenic defect clearly associated with susceptibility, the description of MIS-C in a patient with haploinsufficiency of SOCS1, a monogenic autoimmune/immune dysregulation syndrome, supports a role of cytokine/STAT signaling in control of inflammation after infection in children [53•]. Early studies of SARS-CoV-2 infections in patients with IEIs did not report exacerbation of their autoimmune disease but did suggest that young patients with IEIs were more likely to develop severe symptoms than age-matched controls [61]. More detailed information and collection of immune phenotyping from SARS-CoV-2 infected patients with monogenic autoimmunity will be informative.

Conclusion

Immune dysfunction in IEIs can lead to autoimmune diseases with auto-reactivity of T and B cells, increased activity of the innate immune response, and in some cases increased susceptibility to infection. While T and B cell dysfunction contributes to autoimmune and infectious sequelae, recent studies have brought to light molecular pathways such as abnormalities in IFN and cytokine signaling that contribute to pathogen susceptibility in monogenic autoimmunity. Although there are similarities in the immunologic aberrancies amongst monogenic autoimmune disease, future studies describing the differential effects of specific genes will be needed to resolve why

certain monogenic autoimmune diseases are associated with unique or shared pathogen susceptibility. Certainly, the COVID-19 pandemic has and will continue to provide new insights into the interaction between pathogens and genes that regulate the immune system. New *in vivo* models and advancements in the study of human immunology will also expand our understanding of the impact of genes associated with monogenic autoimmunity on the complex relationship between maintaining self-tolerance and controlling infection.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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Variants in COPA that are associated with COPA syndrome cause STING activation and retention in the Golgi due to failed retrieval by COPI complexes. This is potentially due to failed interaction between STING, COPA and SURF4. In $Copa^{E241K/+}$ knock-in mice, medullary thymic epithelial cells and thymocytes in the medulla show increased expression of ISGs and altered thymocyte development, both of which are dependent on STING expression. This report establishes a potential link between COPA, abnormal STING and IFN signaling, and thymic selection.

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Increased type I IFN signaling was observed in the blood of COPA patients. *In vitro* expression of mutant COPA resulted in a STING-dependent increase in type I IFN signaling as well as accumulation of STING in the Golgi. This study shows a potential pathogenic mechanism whereby variants in COPA lead to type I IFN dysregulation through STING transport.

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A $Copa^{E241K/+}$ knock-in mouse developed interstitial lung disease similar to COPA patients as well as impaired thymic selection resulting in autoreactive T cells, impaired production of antigen-specific (OVA) Tregs, and decreased numbers of Tregs in the periphery. This report establishes the impact of COPA on T cell selection.

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Deficiency of *STIM1* induces STING-dependent type I IFN signaling *in vitro* in mouse and human cells. STIM1 interacts with STING and inhibits its trafficking from the ER. In a mouse model, *STIM1* deficiency decreased HSV-1 genomic GFP expression and murine herpesevirus-68 (MHV68) early and late gene expression *in vitro*, and decreased HSV-1 induced mortality and viral load in the brain, suggesting that loss of *STIM1* impacts viral replication and host defense.

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Whole exome sequencing of patients with early onset autoimmunity revealed heterozygous loss-of-function variants in *SOCS1*. Lymphocytes from these patients demonstrated increased STAT activation after *in vitro* stimulation with IFN-γ, IL-2 and IL-4, which was inhibited by a JAK1/2 inhibitor. This study describes the disease phenotype and immunologic dysfunction associated with *SOCS1* loss-of-function.

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Two patients with autoimmune cytopenias, one of whom developed MIS-C after a SARS-CoV-2 infection, were found to have heterozygous variants in *SOCS1*. PBMCs from these patients exhibited increased STAT1 phosphorylation, type I and II IFN signaling and pro-apoptotic gene expression. This report suggests that disruption of regulation of JAK/STAT signaling is associated with risk of MIS-C.

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Whole genome sequencing of 138 patients with primary immune deficiency, mainly adults, was utilized to identify disease-causing variants in genes and non-coding regulatory regions. Genome-wide association study was also used to establish potential contribution of common variants to monogenic IEI. Functional studies of variants from patients with compound heterozygous common and rare variants in *PTPN2* or *SOCS1*, both of which are negative regulators of STAT signaling, demonstrated potential interaction between common and pathogenic variants.

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This publication reported 22 patients with APS-1 (also known as APECED) due to AIRE deficiency who were infected with SARS-CoV-2. Patients with APS-1 are known to have neutralizing antibodies against type I IFNs, and the patients tested in this cohort all had autoantibodies to IFN-α and/or IFN-ω. In this cohort, a striking 86% of patients were hospitalized for COVID-19 pneumonia and 18% died, suggesting high morbidity and mortality with pre-existing type I IFN antibodies.

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