Anticytokine Autoantibody–Associated Immunodeficiency*

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Abstract

Anticytokine autoantibodies are an emerging mechanism of disease in previously healthy adults. Patients with these syndromes demonstrate a unique infectious phenotype associated with neutralizing autoantibodies that target a specific cytokine. Examples include anti-interferon (IFN)-γ autoantibodies and disseminated nontuberculous mycobacteria; anti-granulocyte macrophage colony–stimulating factor autoantibodies and cryptococcal meningitis; anti-interleukin (IL)-6 autoantibodies and staphylococcal skin infection; and anti-IL-17A, anti-IL-17F, or anti-IL-22 autoantibodies and mucocutaneous candidiasis in the setting of either APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy syndrome) or thymoma. Other anticytokine autoantibodies may contribute to an infectious phenotype such as anti-granulocyte colony stimulating factor and anti-IFN-α autoantibodies, although the strength of the association is less clear. Their identification not only affects disease management but also may uncover key mechanisms of host defense against specific organisms. Furthermore, it raises the possibility that currently idiopathic diseases will someday be explained by a yet unidentified anticytokine autoantibody. This review focuses on the current understanding, both clinical and mechanistic, of anticytokine autoantibody-associated immunodeficiency.

INTRODUCTION

Anticytokine autoantibodies are gaining increasing recognition as important mediators of disease pathogenesis in a variety of potentially life-threatening illnesses. The circumstances are diverse, ranging from disseminated opportunistic infections due to anti-interferon (IFN)-γ autoantibodies (1) to chronic mucocutaneous candidiasis (CMC) associated with anti-interleukin (IL)-17A, anti-IL-17F, or anti-IL-22 (2, 3) autoantibodies (**Figure 1**). The same anticytokine autoantibody can even result in different disease manifestations, exemplified by those targeting granulocyte macrophage colony–stimulating factor (GM-CSF), in which patients may have isolated pulmonary alveolar proteinosis (4), cryptococcal meningitis, or both (5). Because anticytokine autoantibodies are not routinely sought, their natural history prior to presentation of overt disease is hard to discern. It remains unknown in most conditions whether they develop gradually over time or acutely in response to a specific trigger. However, the diagnosis of pathogenic anticytokine autoantibodies

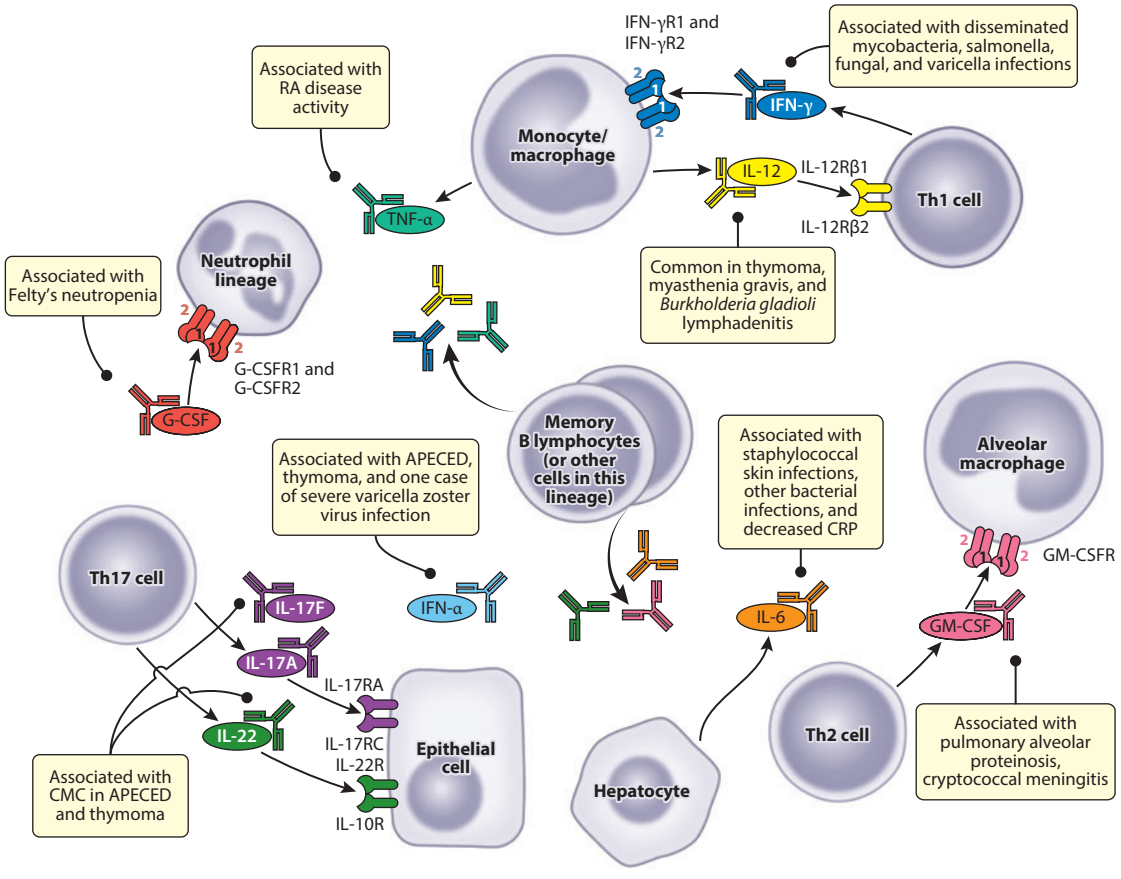

Figure 1

Anticytokine autoantibody–associated syndromes. (Abbreviations: APECED, autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy syndrome; CMC, chronic mucocutaneous candidiasis; CRP, C-reactive protein; G-CSF, granulocyte colony–stimulating factor; GM-CSF, granulocyte macrophage colony–stimulating factor; IFN, interferon; IL, interleukin; RA, rheumatoid arthritis; Th, T helper cell; TNF, tumor necrosis factor.)

should be considered, particularly in the context of unusual or adult-onset infections, especially because their identification may impact clinical management.

Anticytokine autoantibodies have been reported in disparate circumstances far beyond highly pathologic presentations characterized by a specific high-titer, neutralizing anticytokine autoantibody. Naturally occurring autoantibodies against many cytokines have been reported in healthy subjects (6, 7). Many have also been reported in the setting of disease, infectious and otherwise, including anti-IL-2 autoantibodies in HIV (8); anti-IFN-γ autoantibodies in *Mycobacterium tuberculosis* (MTB) (9) and African trypanosomiasis (10); anti-IFN-α autoantibodies in graft-versus-host disease (11) and malignancy (12); anti–tumor necrosis factor-α in patients with gram-negative bacterial septicemia and chronic pulmonary *Pseudomonas* infection, inflammatory diseases (13), and rheumatoid arthritis (RA) (14); and anti-IL-8 autoantibodies in RA (15), ovarian cancer (16), heparin-associated thrombocytopenia (17), and adult respiratory distress syndrome (18). In most instances, their biological activity or role in pathogenesis is unclear, whether it is neutral, destructive, or protective.

Anticytokine autoantibodies may arise in patients receiving exogenously administered cytokines, such as IFN-α for the treatment of hepatitis C (19) or IFN-β for the treatment of multiple sclerosis (20). Again, their presence is of clinical importance given the potential to render cytokine therapy less effective. In the most extreme example, neutralizing anti-erythropoietin (EPO) autoantibodies elicited by exogenous EPO can lead to the severe anemia of pure red cell aplasia (PRCA) (21). Interestingly, postmarketing surveillance recently recognized PRCA in patients with hepatitis C who were concurrently receiving recombinant EPO and IFN-α, implicating a role for IFN-α in autoantibody production beyond its own antigenicity.

This review focuses specifically on the infection-associated anticytokine autoantibody disorders, while recognizing that anticytokine autoantibodies may be important across many other diseases. I discuss the strength of the association, highlighting the in vitro and in vivo evidence for their pathogenicity and the mechanisms thought to underlie their clinical features (**Table 1**), as well as aspects of diagnosis and management. Diseases specifically associated with anticytokine autoantibodies, including autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) and thymoma, are addressed. Plasma and serum appear equally useful for detection and characterization of anticytokine autoantibodies and are used interchangeably for the purposes of this discussion.

ANTI–GRANULOCYTE MACROPHAGE COLONY–STIMULATING FACTOR AUTOANTIBODIES

The GM-CSF receptor is a tetrameric molecule composed of α and β subunits in duplicate, which together bind two GM-CSF molecules with high affinity (22). GM-CSF receptor-ligand interaction induces signal transduction and activator of transcription (STAT)-5 phosphorylation, nuclear translocation, and induction of master transcription factor PU.1. Together, GM-CSF and PU.1 are essential for surfactant catabolism in the pulmonary alveoli, and both augment innate immunity (23–26). Pulmonary alveolar proteinosis (PAP) was first described in 1958 by Rosen et al. (27) as an idiopathic syndrome of respiratory failure, histopathologically characterized by alveolar filling with acellular periodic acid-Schiff-positive proteinaceous material. However, its association with defective GM-CSF signaling remained unknown for nearly four decades.

Clues as to the etiology of PAP emerged in 1994 and 1995 when it was reported that GM-CSF-null and GM-CSF receptor β–null mice (28, 29) developed lung disease that was highly reminiscent of human PAP. Shortly after, a severe and early-onset form, primary PAP, was linked to Mendelian defects in the β (30) and, later, the α (31, 32) GM-CSF receptor subunits.

Table 1 Laboratory and clinical associations with anticytokine autoantibodies[a]

Anticytokine autoantibody target	Biological rationale	In vitro evidence	Associated infections	Clinical associations	Treatment	Comments
GM-CSF	Mutations in GM-CSF receptor A (31, 148) or B (30) lead to similar pediatric-onset phenotype (primary PAP). GM-CSF cytokine and receptor knockout mouse models develop PAP (29, 149).	Anti-GM-CSF autoantibodies inhibit GM-CSF-induced pSTAT5 production (5), RNA expression including transcription factor PU.1 (24, 26), and protein expression such as MIP-1α. Introduction of GM-CSF autoantibodies to nonhuman primates causes PAP (150).	*Cryptococcus* spp. (5), *Nocardia asteroides* (41, 46, 49), *Mycobacterium avium* complex (43), *Proteus* (56)	PAP, meningitis	Whole-lung lavage, exogenous GM-CSF (inhaled or subcutaneous), rituximab	Cryptococcal meningitis may present before or in absence of PAP
IFN-γ	Patients with mutations in the IFN-γ-IL-12 signaling axis (IFNγR, STAT1, IL-12R, IL-12p40) develop infections with NTM and intracellular pathogens (62, 65).	Anti-IFN-γ autoantibodies prevent IFN-γ-induced pSTAT1 (74). Antibody-containing plasma or IgG prevents RNA expression and protein production in normal PBMC (67, 72).	NTM (rapid and slow growers), MTB, *Salmonella*, *Cryptococcus*, *Histoplasma*, *Penicillium* (all disseminated), varicella zoster reactivation (localized and disseminated) (1, 77)	Hypergammaglobulinemia, elevated inflammatory markers, anemia, neutrophilic dermatosis	Anti-infectives, rituximab (four patients) (69), plasmapheresis and cyclophosphamide (one patient) (68)	Predilection in Asia-born Asians
IL-17A	Patients with mutations in IL-17F and IL-17RA (83) and those with genetic mutations that lead to defects in Th17 population (IL-12Rβ1, STAT3, CARD9, Dectin-1) (146) are all predisposed to CMC.	Anti-IL-17 autoantibodies prevent IL-17-induced IL-6 in HFF-1 cells.	CMC (2, 3)	APECED, thymoma	Topical or systemic antifungals	Unclear degree to which quantitative and qualitative Th17 defects contribute to pathogenesis of CMC

IL-17F	(See IL-17A above)	(See IL-17A above)	CMC (2, 3)	APECED and thymoma	Topical or systemic antifungals	IL-17A and F form homo- and heterodimers and appear to have overlapping immunological roles
IL-22	IL-22 is produced by Th17 cells and stimulates production of antimicrobial peptides; it is thought to play a role in mucosal immunity (151).	No functional testing reported	CMC (2, 3)	APECED and thymoma	Topical or systemic antifungals	
G-CSF	G-CSF promotes proliferation and differentiation of cells within the neutrophil lineage (97).	Some anti-G-CSF autoantibody–containing plasma can prevent G-CSF-induced cell proliferation in a G-CSF-dependent cell line (100).	None	Felty's syndrome; SLE (100)	None	Only one report to date
IL-6	IL-6 promotes acute-phase response to infection; patients with mutations in STAT3 (downstream of IL-6) suffer staphylococcal skin infections (95).	Patient serum blocks IL-6 detection and prevents IL-6-induced pSTAT3 (94); in vivo, patients with IL-6 autoantibodies demonstrate undetectable CRP (93, 94).	*Staphylococcus aureus* (93, 94), *Streptococcus intermedius* and *Escherichia coli* (93), bacterial sepsis (92)	One report identifies anti-IL-6 autoantibodies in alcoholic liver disease as an independent risk factor for mortality (92)	Anti-infectives	

(*Continued*)

Table 1 (*Continued*)

Anticytokine autoantibody target	Biological rationale	In vitro evidence	Associated infections	Clinical associations	Treatment	Comments
IL-12p70	One case of IL-12Rβ1 mutation and *Burkholderia cepacia* identified (S.K. Browne, manuscript in progress).	Anti-IL-12p70 autoantibodies prevent IL-12-induced pSTAT4 production and IFN-γ production.	*Burkholderia gladioli*	Thymoma and myasthenia gravis	Anti-infectives	Only one case directly associated with infection; neutralizing anti-IL-12 autoantibodies reported in thymoma and myasthenia gravis with unclear infectious consequences
Type I IFNs	These IFNs are important in the control of viral infections that may play a role in pathogenesis of autoimmune diseases (123).	Anti-IFN-α autoantibodies prevent IFN-α-induced pSTAT1 (108) and are associated with decreased expression of IFN-responsive genes (118).	Varicella zoster virus (117)	Thymoma (132), APECED (116), autoimmune disease, many others	IFN-α given to the patient with disseminated zoster	Disseminated zoster also reported in patients with thymoma (108) and neutralizing anti-IFN-α autoantibodies

[a]Abbreviations: APECED, autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy; CMC, chronic mucocutaneous candidiasis; CRP, C-reactive protein; G-CSF, granulocyte colony–stimulating factor; GM-CSF, granulocyte macrophage colony–stimulating factor; HFF, human foreskin fibroblast; IFN, interferon; MTB, *Mycobacterium tuberculosis*; NTM, nontuberculous mycobacteria; PAP, pulmonary alveolar proteinosis; PBMC, peripheral blood mononuclear cell; SLE, systemic lupus erythematosus; STAT, signal transduction and activator of transcription; Th, T helper cell.

Contemporaneously, a neutralizing anti-GM-CSF IgG was identified in association with acquired PAP (33, 34). In contrast to the primary disorder, the median age of diagnosis of the autoimmune form is 39, after a median of 7 months of insidiously progressive cough and dyspnea. Its clinical course and severity are highly variable, ranging from progressive respiratory decline to chronic persistence and spontaneous resolution (35). By contrast, secondary PAP results from qualitative or quantitative alveolar macrophage deficiencies (36) and is generally linked to hematologic malignancies, iatrogenic immunosuppression, inhaled toxins, and, most recently, GATA-2 deficiency (37).

Of the three forms of PAP, autoimmune is by far the most common, representing approximately 90% of cases. Impaired catabolism of surfactant as a result of GM-CSF inhibition likely explains the decreased clearance and subsequent overaccumulation of surfactant in pulmonary alveoli (38). Evidence from GM-CSF receptor–deficient mice suggests that GM-CSF induces *PU.1*, a gene critical to surfactant homeostasis (26). Bonfield et al. (24) subsequently showed decreased PU.1 mRNA in cells isolated from bronchoalveolar lavage from patients with PAP, thereby confirming that anti-GM-CSF autoantibodies affect events downstream of GM-CSF signaling.

Although the primary pathological process relates to impairment of GM-CSF-dependent catabolism of surfactant in pulmonary alveoli (38), opportunistic infections have been observed in patients with PAP, dating as far back as its original description (27). Beyond its role in pulmonary surfactant homeostasis, GM-CSF in both humans and mice facilitates a multitude of innate immune responses (24–26). In fact, PU.1 not only is central to the pulmonary aspects of PAP (24), but also regulates TLR signaling, adhesion, phagocytosis, and microbicidal activity (26), linking anti-GM-CSF autoantibodies to both PAP and infection susceptibility. Beyond macrophage dysfunction, defects have been observed in neutrophil adhesion, phagocytosis, oxidative burst, and bacterial killing from both human PAP patient blood and GM-CSF-null mouse bone marrow (39), thereby expanding the spectrum of organisms to which patients may be vulnerable.

Patients with acquired PAP are prone to typical respiratory pathogens as well as to opportunistic infections. Although the high incidence of respiratory infections may be partially attributable to their underlying chronic lung disease, the opportunistic infections are generally with organisms controlled by phagocytes including *Nocardia* (27, 40, 41), nontuberculous mycobacteria (NTM) (42, 43), histoplasma (44), and cryptococcus (5, 27). However, these associations are not clear-cut. The largest series of patients with PAP and NTM included eight patients with *Mycobacterium avium* complex cultured from bronchoalveolar lavage fluid, who were not treated with antimycobacterials and suffered no apparent clinical consequence (43), suggesting possible colonization rather than infection. Furthermore, the majority of infections were reported before anti-GM-CSF autoantibodies were identified as causing PAP, thereby introducing heterogeneity into the underlying diagnosis.

Extrapulmonary infections have been observed with some frequency and could relate to the systemic effects of anti-GM-CSF autoantibodies identified in serum (45). Several case reports describe patients with PAP who had extrapulmonary infections including five cases of central nervous system (CNS) *Nocardia* (46–50), septic arthritis (51), perinephric abscess (52), and *Nocardia* dissemination to skin (53); CNS *Aspergillus* (54) and *Proteus* (55, 56); and three cases of disseminated histoplasmosis (44). Recently, seven cases of cryptococcal meningitis were associated with anti-GM-CSF autoantibodies (5) and three cases of CNS nocardiosis (L.B. Rosen, N. Rocha Pereira, C. Figueiredo, L. Fiske, R.A. Ressner, J. Hong, S.M. Holland, S.K. Browne, manuscript submitted), none of whom had concurrent PAP, although one patient developed it later. Why the same autoantibody may have different clinical phenotypes is unknown. Perhaps the differential effects relate to differences in the GM-CSF epitope being recognized. Alternatively, it may take a less inhibitory antibody to confer infection susceptibility than it does to cause PAP. Furthermore, it appears that

only a specific serotype of *Cryptococcus neoformans* is linked to GM-CSF autoantibodies and meningitis (T. Saijo, J. Chen, S.C.-A. Chen, L.B. Rosen, T.C. Sorrell, J.E. Bennett, S.M. Holland, S.K. Browne, and K.J. Kwon-Chung, manuscript submitted). Thus, the concurrence of anti-GM-CSF autoantibodies and outdoor exposure to a sufficient inoculum of the right organism (particularly if patient mobility is compromised by a debilitating lung disease) may be an infrequent event.

Treatment has targeted both the consequences of the autoantibody as well as the anti-GM-CSF autoantibody itself. Whole-lung lavage has been employed to remove the accumulation of proteinaceous material from the alveoli. Inhaled and subcutaneous GM-CSF were each effective in two large studies (57–59). It is unclear whether such treatment works by saturating the autoantibody or inducing tolerance, but the fact that GM-CSF administration does not influence anti-GM-CSF autoantibody titers supports the former. B cell–directed therapy targeting autoantibody production with the anti-CD20 biological rituximab has also yielded encouraging results in smaller studies (60, 61).

ANTI-IFN-γ AUTOANTIBODIES

IFN-γ, produced largely by T helper 1 (Th1) and natural killer cells, is central to host defense against intracellular pathogens. The IFN-γ receptor (IFNγR) consists of IFNγR1 and IFNγR2 subunits, which combine in duplicate, to form a tetramer, and bind IFN-γ. IFN-γ ligand-receptor interaction leads to JAK2 and then JAK1 phosphorylation on the intracellular portions of IFNγR2 and IFNγR1, respectively. STAT1 docks on the intracytoplasmic domain of each IFNγR1, is phosphorylated, homodimerizes, and translocates to the nucleus. Transcription of IFN-responsive genes that facilitate macrophage differentiation and activation leads to elaboration of inflammatory mediators. The IFN-γ and IL-12 pathways are critical for defense against certain pathogens: Genetic defects along these pathways, including the IFNγR1, IFNγR2, IL-12p40, and IL-12Rβ1 pathways as well as related molecules STAT1, NEMO (62), IRF8 (63), and ISG15 (64), confer similar phenotypes of infection susceptibility. Not surprisingly, infections in patients with these defects involve organisms that are controlled by macrophages and include disseminated infections with mycobacteria (both MTB and NTM), listeriosis, salmonellosis, histoplasmosis, melioidosis, and penicilliosis (62, 65). Neutralizing anti-IFN-γ autoantibodies in association with disseminated NTM infection were first reported in 2004, representing an alternative mechanism by which the IFN-γ-IL-12 axis is disrupted (66, 67) and conferring a similar pattern of infection susceptibility. Since then, more than 130 patients have been reported (66–77). The largest study enrolled 85 patients in 6 months, suggesting anti-IFN-γ autoantibody–associated immunodeficiency is probably underappreciated.

Anti-IFN-γ autoantibodies have been reported in the context of other infections as well (9, 10). Madariaga et al. (9) identified anti-IFN-γ autoantibodies in otherwise normal individuals infected with MTB. The highest levels of autoantibodies to IFN-γ were found in MTB patients with recent latent tuberculosis infection, followed by patients with severe active MTB. Interestingly, autoantibody titers correlated with serum IFN-γ levels. The functionality of these autoantibodies was not assessed. Thus, it remains unknown if the autoantibodies were inhibitory, inactive, or activating; whether they were beneficial, neutral, or detrimental; and ultimately how those properties influenced the clinical course.

The adult-onset immunodeficiency due to anti-IFN-γ autoantibodies differs from prior reports of anti-IFN-γ autoantibodies in the context of infectious diseases such as pulmonary tuberculosis (9) or African trypanosomiasis (10) in that the autoantibodies in this syndrome are extremely high titer and block IFN-γ at many levels including IFNγR signaling, gene expression, and protein production (67, 68, 72, 74). Further evidence that these autoantibodies

are pathophysiologically important is that the associated opportunistic infections, including disseminated NTM, MTB, *Salmonella*, *Penicillium*, *Histoplasma*, *Cryptococcus*, and *Burkholderia pseudomallei*, resemble those observed in patients with genetic defects in the IFN-γ-IL-12 axis. Any organ system may be involved, although lymph nodes, skin, soft tissue, and bone appear to be frequently affected. Patients with anti-IFN-γ autoantibodies also appear to experience both dermatomal and disseminated varicella zoster reactivation at higher frequency (1, 77). Reactive dermatoses, most commonly neutrophilic dermatosis, but also erythema nodosum, pustular psoriasis, and exanthematous pustulosis, are common.

All reported cases of patients with anti-IFN-γ autoantibodies were previously healthy adults, most of whom were Asia-born Asians. Recently, a strong association with HLA-DRβ1602 and -DRβ0502 was shown in 17 patients with anti-IFN-γ autoantibodies (70), further implicating genetic risk factors for disease. However, given that even the largest cohort of patients identified no familial clustering, the genetics are likely complex. Furthermore, few if any cases have been reported in Asians born outside of Asia (although they may have emigrated in childhood), suggesting that environmental factors, possibly early in life, may contribute to the development of this syndrome.

Patients often have laboratory features indicative of chronic inflammation or infection, including anemia, leukocytosis, elevated erythrocyte sedimentation rate, C-reactive protein (CRP), and/or β2-microglobulin and a polyclonal hypergammaglobulinemia. Otherwise, they generally have grossly normal immunologic parameters, including $CD4^+$ T lymphocytes, monocyte numbers, and IFNγR1 expression, although subtle perturbations in other lymphocyte subsets of unclear significance have been observed (1).

The primary treatment involves targeted antimicrobials to manage the infections. NTM tends to be the most recalcitrant to therapy, often requiring multiple drugs for months to years; secondary prophylaxis may be continued indefinitely. In cases refractory to anti-infective agents, some have attempted to overcome the anti-IFN-γ antibody by giving exogenous IFN-γ. However, this approach has appeared less helpful than the analogous approach of using GM-CSF administration in PAP, perhaps because the anti-IFN-γ autoantibody levels are often much higher titer than anti-GM-CSF autoantibodies (S.K. Browne, unpublished data). Others have attempted to drive down autoantibody levels with plasmapheresis and, in one case, cyclophosphamide (68). Use of rituximab was reported in a series of four cases, all of which responded clinically, with commensurate decrease in anti-IFN-γ autoantibody levels and neutralizing capacity (69). It is unclear which factors predict response to antimicrobials alone versus the need for further immunomodulation. Future well-controlled studies are needed to evaluate the safety and efficacy of these approaches.

ANTI-IL-17A, ANTI-IL-17F, AND ANTI-IL-22 AUTOANTIBODIES

IL-17A and IL-17F are the two most abundant and well characterized of the six IL-17 family cytokines (A through F) and have been linked to inflammation and autoimmunity. IL-17A and IL-17F homodimers as well as IL-17A/F heterodimers bind a receptor composed of two subunits, IL-17RA and IL-17RC, which leads to nuclear factor (NF)-κB activation. IL-22 is produced largely by T lymphocytes and natural killer cells. Its receptor is also a dimer, composed of IL-22R1 and IL-10R2, and is found primarily on epithelial and other nonimmune cells. IL-17A, IL-17F, and IL-22 cooperate to induce proinflammatory cytokines involved in granulopoiesis, neutrophil recruitment, and production of antimicrobial peptides, such as β defensins and S100 proteins, which are thought to be important in mucosal immunity (78). CMC has been observed in various diseases of Mendelian inheritance, including STAT3-deficient hyper-IgE (Job's) syndrome (79, 80), dectin-1 deficiency (81), CARD9 deficiency (82), and IL-12Rβ1 deficiency (79),

which share varying degrees of impaired Th17 activity. Subsequently, two families, one with an autosomal recessive mutation in the IL-17RA and another with an autosomal-dominant negative mutation in IL-17F (83), demonstrated severe CMC disease, strengthening the association between IL-17 activity and mucosal immunity to *Candida*. Together, these observations support a causal relationship among anti-IL-17A, anti-IL-17F, and anti-IL-22 autoantibodies that has been observed in association with CMC.

Thus far, all cases of anti-IL-17A, anti-IL-17F, or anti-IL-22 autoantibody–associated CMC have been identified in patients with either APECED or thymoma. APECED, caused by mutations in the autoimmune regulator (AIRE) gene (84), classically leads to a clinical triad of hypoparathyroidism, adrenal insufficiency, and CMC, although many autoimmune complications have been reported. AIRE is critical for negative selection of autoreactive T cells in the thymus (85), explaining the strong propensity for autoimmune disease. Given that the fundamental defect in this disorder involves T cell education, the T cell defects are profound, including provision of T cell help, which could explain the tendency to develop autoantibodies. Similarly, thymoma, another disease of the thymus that is highly associated with both autoimmunity and autoantibodies, has demonstrated defective AIRE expression (86, 87) and autoantibody production. The exact role AIRE is playing in pathogenesis of organ-specific autoimmunity and autoantibody production has not been fully clarified, as there is still considerable clinical diversity among patients with APECED and thymoma (87).

Thus, unlike most inherited immunodeficiencies, CMC in APECED is not directly linked to AIRE deficiency, but rather to production of neutralizing anti-IL-17A, anti-IL-17F, and anti-IL-22 autoantibodies (2, 3). Puel et al. (3) identified autoantibodies against IL-17A, IL-17F, or IL-22 in 33 APECED patients, 29 of whom also had CMC, compared with healthy controls who had neither autoantibodies nor CMC. Kisand et al. (2) found anti-IL-17A, anti-IL-17F, or anti-IL-22 autoantibodies in up to 90% of 162 cases that were also strongly associated with CMC. They also identified anti-IL-17 and anti-IL-22 autoantibodies in two patients with thymoma and CMC, but in none of the 33 thymoma patients without CMC. There were a few instances of autoantibodies without CMC, as well as CMC without autoantibodies, suggesting that autoantibodies to IL-17 and IL-22 do not explain the CMC in its entirety. Global defects were demonstrated in the ability of Th17 cells to respond to T cell agonists (including *Candida*) and produce IL-17 (2). Outside of APECED and thymoma, most cases of CMC are found in defective cell-mediated immunodeficiency (HIV infection, severe combined immunodeficiency, iatrogenic T cell immunosuppression). Similarly, patients with thymoma have long been known to suffer from infections that are also suggestive of T cell immunodeficiency such as cytomegalovirus and pneumocystis pneumonia (88). Nevertheless, the fact that both patients with autoantibodies to IL-17 and families with IL-17RA and IL-17F mutations develop CMC strongly suggests a causal relationship, even if there may be varying degrees of other contributing factors in some patients.

ANTI-IL-6 AUTOANTIBODIES

IL-6 is produced by immune and nonimmune cells including B cells, T cells, macrophages, synovial cells, endothelial cells, and hepatocytes. It may be involved in the acute-phase response and lymphocyte activation, linking innate and acquired immunity. It is also an important mediator of chronic diseases such as RA and Crohn's disease (89). IL-6 signals through a heterodimeric receptor, binding the IL-6Rα subunit and transducing signal via a second shared subunit, gp130. IL-6 regulates the acute-phase response in the liver, with its hallmark induction of CRP and elevated erythrocyte sedimentation rate. Autoantibodies to IL-6 have been identified both in healthy controls (90, 91) and in association with bacterial infection (92–94).

Anti-IL-6 autoantibodies were identified in association with severe bacterial infections first in patents with alcoholic cirrhosis (92) and then in three otherwise immunocompetent hosts (93, 94). In the first series, the authors (92) identified anti-IL-6 autoantibodies as an independent risk factor for mortality in alcoholic cirrhosis and recurrent infection. However, the levels of autoantibodies measured were at least 2–3 log lower than those seen in other anticytokine autoantibody–associated diseases, and no evidence was presented for direct functionality, such as plasma CRP levels or the ability of the antibodies to neutralize IL-6 in vitro. The patients also had normal or elevated plasma levels of IL-6, lending uncertainty to the physiological significance of the identified autoantibodies. More recently, neutralizing anti-IL-6 autoantibodies were identified in a 3-year-old Haitian boy who twice developed severe staphylococcal cellulitis, one complicating chickenpox infection and the other complicating mosquito bites (94). Two additional adult patients have been reported since, one with severe staphylococcal skin abscesses and one who succumbed to a thoracic empyema caused by *Escherichia coli* and *Streptococcus intermedius* (93). Treatment included supportive care and anti-infective agents. All three cases had undetectable CRP, despite severe infection, which suggested impaired IL-6 activity. Plasma from each patient blocked IL-6 activity in vitro, whereas their cells, washed of plasma, had normal IL-6 production. IL-6 signals through STAT3, and autosomal-dominant mutations in STAT3 lead to recurrent staphylococcal skin abscesses as well as to recurrent lung infections (95), suggesting a potential overlap in the clinical phenotype between the patients with STAT3 deficiency and neutralizing anti-IL-6 autoantibodies.

AUTOANTIBODIES TO GRANULOCYTE COLONY-STIMULATING FACTOR

Granulocyte colony-stimulating factor (G-CSF) is produced by bone marrow stromal cells at a low level that can increase during physiologic stress, such as bacterial infection or low absolute neutrophil counts (96). The homodimeric receptor, G-CSFR, is found on many cells of myeloid lineage as well as on nonimmune cells, but it appears most highly expressed and physiologically important in its action on cells within the neutrophil lineage. G-CSFR activation causes multiple signaling cascades that lead to phosphorylation of STAT1, STAT3, and STAT5 homo- and heterodimerization as well as MAPK and PI3K activation (97). In addition to the critical roles neutrophils play in innate immunity and antimicrobial defense, they also contribute to tissue destruction and chronic inflammation (98).

The first description of anti-G-CSF autoantibodies was in the setting of hematologic malignancy. The authors (99) identified endogenous anti-G-CSF autoantibodies in 1 of 12 patients and 15 of 135 controls. Recombinant G-CSF for chemotherapy-induced neutropenia increased the anti-G-CSF autoantibodies in that single patient and led to identification of anti-G-CSF autoantibodies in 3 additional patients. Neutralizing activity was not assessed, and the autoantibodies did not appear to interfere with neutrophil recovery.

Anti-G-CSF autoantibodies were later identified in Felty's syndrome (FS), the triad of RA, splenomegaly and neutropenia, and systemic lupus erythematosus (SLE). The authors (100) identified anti-G-CSF autoantibodies in 11 of 15 patients with FS, whereas no patients with RA alone had them. They identified equal numbers of anti-G-CSF IgG in SLE patients with and without neutropenia (6 out of 16 patients per group). The autoantibodies were low titer compared with other anticytokine autoantibody–associated syndromes. In vitro evaluation demonstrated that, whereas some anti-G-CSF autoantibody–containing IgG inhibited G-CSF activity, others appeared to have no effect or possibly stimulatory effects. Although neutropenia in FS is associated with bacterial infections (101, 102), the authors (100) did not evaluate for an association between infection and anti-G-CSF autoantibodies. Many other anticytokine autoantibodies have

been described in the rheumatologic conditions (103), although their physiologic role in disease pathogenesis or amelioration thereof has yet to be defined.

ANTI-IL-12P70 AUTOANTIBODIES

IL-12p70 is a heterodimeric molecule consisting of IL-12p35 and IL-12p40 subunits; it signals through a heterodimeric receptor complex of IL-12Rβ1 and IL-12Rβ2 (104). IL-12 ligand-receptor binding leads to docking of TYK2 and JAK2 on IL-12Rβ1 and IL-12Rβ2, respectively. TYK2 and JAK2 are phosphorylated, leading to docking and phosphorylation of STAT4, which homodimerizes, translocates to the nucleus, and initiates transcription of target genes including those that encode IFN-γ. IL-12, in concert with IFN-γ, plays an important role in host defense against intracellular pathogens, as evidenced by Mendelian defects in IL-12p40 and IL-12Rβ1, which lead to opportunistic infection with intracellular pathogens (105, 106). Thus, just as anti-IFN-γ autoantibodies present as a phenocopy of Mendelian defects within this signaling pathway, patients with anti-IL-12 autoantibodies may suffer a similar fate. Interestingly, however, this has not been borne out clinically, as many patients, particularly those with thymoma or myasthenia gravis (MG), have high-titer neutralizing anti-IL-12 autoantibodies but no clinically overt infections.

Recently, one patient of Cambodian ethnicity presented with severe recurrent *Burkholderia gladioli* lymphadenitis and was demonstrated to have isolated neutralizing anti-IL-12p70 autoantibodies as the only identifiable immune defect or medical problem (107). Similar to many patients with thymoma (108), her plasma prevented IL-12-induced pSTAT4 in normal peripheral blood mononuclear cells as well as IL-12-induced IFN-γ production. Interestingly, a patient with *Burkholderia cepacia* bacteremia and lymphadenitis was found to have an IL-12Bβ1 mutation (S.M. Holland, personal communication). If her anti-IL-12 autoantibody plays a role in this unusual infection, there is precedent for a differential effect by the same anticytokine autoantibody, as in the cases of patients with anti-GM-CSF autoantibodies who develop cryptococcal meningitis or CNS nocardiosis but not PAP (5; L.B. Rosen, N. Rocha Pereira, C. Figueiredo, L. Fiske, R.A. Ressner, J. Hong, S.M. Holland, and S.K. Browne, manuscript submitted). Alternatively, the anti-IL-12 autoantibody may be contributing a "second hit" to a subtle preexisting immune defect. As more unexplained cases of extrapulmonary *Burkholderia* are identified, outside of known risk factors such as chronic granulomatous disease, it will be important to interrogate the IL-12 pathway.

ANTI–TYPE I INTERFERON AUTOANTIBODIES

The type I IFNs, including IFN-α, IFN-β, and IFN-ω, are generated by somatic and immune cells including T cells, B cells, natural killer cells, and dendritic cells (DCs) in response to viruses and stimulation of certain TLRs. All type I IFNs signal through the IFN-α/β receptor (IFNα/βR), which is composed of two subunits, IFNαR1 and IFNαR2. Type I IFN binding to an IFNα/β receptor results in phosphorylation of JAK1 and TYK2, which are associated with IFNαR2 and IFNαR1, respectively (109). Phosphorylated STAT1/STAT2 heterodimers result, translocate to the nucleus, and transcribe type I IFN–inducible genes. Autoantibodies to type I IFNs have been described in healthy donors (110) as well as in association with autoimmune diseases (111), malignancy (112), thymoma (113–115), and APECED (116). One case of neutralizing anti-IFN-α autoantibodies was described in an otherwise healthy patient with dermatomal varicella zoster reactivation that progressed to disseminated infection (117). High-titer neutralizing autoantibodies to IFN-α and IFN-ω occur in APECED and thymoma and inhibit expression of IFN-responsive genes (108, 118). Autoantibodies against type I IFNs were the first endogenous anticytokine autoantibodies to be described in association with autoimmune diseases (111, 119, 120) with

particular focus on SLE (121, 122). Given the high IFN signature observed in SLE (123), anti-IFN-α autoantibodies may have important effects that are either protective or pathophysiological, although investigations around this question have been limited.

AUTOIMMUNE POLYENDOCRINOPATHY, CANDIDIASIS, ECTODERMAL DYSTROPHY SYNDROME

APECED, also known as type I autoimmune polyendocrinopathy syndrome, is a rare, autosomal recessive disorder caused by mutations in the AIRE gene (84). Expression of AIRE has been localized predominantly to medullary thymic epithelial cells and to a far lesser extent to peripheral lymphoid organs (124). Thymic expression of tissue-specific antigens promotes self-tolerance through intrathymic deletion of autoreactive T cells, thereby preventing their escape to the periphery (125). Dysfunction of this process results in autoimmunity, as seen in humans with biallelic mutations in AIRE and in AIRE-deficient mice (85).

APECED is more common among certain ethnic populations including Iranian Jews, Sardinians, and Finns. Genotypic differences and underlying genetic background associated with these specific populations may account for the phenotypic differences observed between them. Prior to the ability to make a molecular diagnosis, the syndrome was recognized for its tendency to present in early childhood as a clinical triad, often starting with candidiasis followed by hypoparathyroidism and then Addison's disease. Features may continue to develop into the sixth decade, the manifestations of which include diabetes mellitus, hypothyroidism, hypogonadism, Sjögren's syndrome, RA, hepatitis, chronic diarrhea, keratitis, vitiligo, pernicious anemia, alopecia, asplenia, tubulointerstitial nephritis, and obstructive lung disease (126, 127). Organ-specific autoantibodies are associated with many of these conditions, with variable evidence, depending on the target, of a direct role in pathogenesis.

In addition to a preponderance of organ-specific autoantibodies and autoimmunity, a high prevalence of anti–type I IFN autoantibodies (116) as well as anti-IL-17A, anti-IL-17F, and anti-IL-22 autoantibodies (2, 3) has been recognized. Although the biological consequences of anti–type I IFN autoantibodies are unclear, anti-IL-17 and anti-IL-22 autoantibodies have been implicated in the development of mucocutaneous candidiasis. Other infectious complications have been reported (128, 129), raising the possibility that anticytokine autoantibodies may occasionally act in concert to propagate unusual or severe infections, but this remains to be systematically evaluated.

THYMIC EPITHELIAL TUMORS

The thymus is central to the process of T cell education, which includes positive and negative selection of T cells. Thymic dysfunction arising from thymic epithelial tumors (TET) including thymoma, atypical thymoma, and thymic carcinoma likely explains the propensity for immunodeficiency and autoimmunity in these diseases (130). In particular, MG, a syndrome of neuromuscular weakness caused by antibodies targeting proteins at the neuromuscular junction, most commonly the acetylcholine receptor, is the most common autoimmune condition associated with TET (131). Numerous reports describe autoantibodies to IL-12 and type I IFNs, which are associated with MG, thymoma, or both (114, 115, 132), although their role in infection susceptibility has not been clearly defined. Similar to APECED, patients with thymoma-associated CMC have demonstrated anti-IL-17 or IL-22 autoantibodies (2, 108). Further linking thymoma, APECED, and anticytokine autoantibodies is the evidence for decreased AIRE expression in thymoma. Offerhaus et al. (133) demonstrated lack of AIRE expression in

thymic tissue from three patients with graft-versus-host disease who had not had hematopoietic stem cell transplantation, implicating acquired failure of thymic AIRE expression as the cause of the failure to delete autoreactive T cells. Presence of anticytokine autoantibodies is associated with opportunistic infections, although the highly variable anticytokine autoantibody profiles and the diverse clinical phenotypes combined with the overall rarity of thymoma have made direct causality between specific anticytokine autoantibodies and clinical phenotype difficult to establish.

Although autoantibodies to IL-12 and IFN-α are elaborated in association with MG and thymoma (132), no specific infection has been etiologically linked with these autoantibodies. Good's syndrome describes a condition of immunodeficiency in patients with thymoma. Good's syndrome patients classically demonstrate hypogammaglobulinemia (134) and variable lymphopenia as the proposed mechanism of immunodeficiency, although anticytokine autoantibodies have not been systematically sought. Infections reported in patients with Good's syndrome include cytomegalovirus colitis and retinitis, severe sinopulmonary infections, mucocutaneous candidiasis, and *Pneumocystis jirovecii* (88). Interestingly, patients with thymoma may have these immunologic parameters with no infection or may have infection without gross immunological abnormalities. Anticytokine autoantibodies also appear to be associated with infection in patients with thymoma, even in the absence of Good's syndrome (108). There may be multiple mechanisms, both cellular and/or humoral, leading to infection susceptibility. In some cases, multiple autoantibodies could act synergistically to inhibit immunoprotective cytokine pathways, but further investigation will be necessary to define these relationships.

DIAGNOSIS

One of the difficulties in studying and managing anticytokine autoantibody–associated diseases is the lack of standardization of diagnostic testing. Most assays are available only on a research basis within individual laboratories. Furthermore, once identified, testing for in vitro blocking (or activating) (135, 136) activity is critical to provide supportive evidence that the anticytokine autoantibody is biologically relevant. Although there are a variety of specific approaches, the general detection strategy uses a specific cytokine as the bait, with some detection method (such as fluorescence or radioactivity) linked to the cytokine. Evaluation of activity requires demonstration that the autoantibody (or plasma containing the autoantibody) blocks or stimulates specific activity of the target cytokine.

Immunoblot with recombinant cytokine using sodium dodecyl sulfate polyacrylamide gel electrophoresis has been used (74). Once the protein is transferred to a nitrocellulose or polyvinylidene fluoride membrane, it can be blotted using plasma as the primary antibody and an antihuman IgG as a secondary. The strengths of this strategy are that it is relatively inexpensive and requires minimal novel technology. The drawbacks are that it is cumbersome, may miss autoantibodies that recognize only conformational epitopes, and is not quantitative.

Radioimmunoassay (RIA) (137) and luciferase immunoprecipitation systems (LIPS) (108) use a protein expression system to directly label the cytokine bait either by labeling [^{35}S]-methionine or by fusing the cytokine to a luciferase reporter, respectively. The labeled cytokine bait is incubated with plasma, and total IgG is captured using protein A and/or G sepharose beads. The amount of radioactivity (RIA) or fluorescence (LIPS) detected on the captured IgG is a function of the specific antibody titer. These assays are sensitive and specific, although in the case of RIA, use of radioactive reagents is required.

ELISA and luminex technology are based on the same concept in which the cytokine bait first is either bound to a microtiter plate (ELISA) or amide-coupled to a bead and then incubated with plasma or IgG (138). Once the plate or beads are washed, only antibody that recognizes the

cytokine remains. To quantify the amount of cytokine-bound antibody, an antihuman IgG is used that is conjugated either to a chemiluminescent molecule (HRP or alkaline phosphatase) in ELISA or to a phycoerythrin-labeled antihuman IgG in the luminex-based assay. The degree of chemiluminescence or fluorescence is a function of the antibody titer. Similar to immunoblot, ELISA is advantageous because it can be performed in most labs and in resource-limited settings. Both approaches can be quantitative by comparison to a standard curve. The luminex-based approach requires access to an appropriate instrument but is rapid and inexpensive once that contingency is met. Because each cytokine may be conjugated to differentially fluorescing microspheres, autoantibody screening can be multiplexed with minimal plasma requirements.

Once an anticytokine autoantibody is identified, many approaches have been used to determine the functionality of anticytokine autoantibodies. These evaluations lend further (but not definitive) evidence of biological importance, because some anticytokine autoantibodies are biologically active despite no direct disease associations (139) and others are present but do not appear biologically active. In general, the approach is to demonstrate that anticytokine autoantibody–containing IgG or plasma prevents the activity of the targeted cytokine in either primary cells or a cell line. Readouts for cytokine activity can include activation of cytokine-induced signal transduction, for example, phosphoprotein detection using flow or immunoblot (74, 108); mRNA expression using quantitative reverse transcription–polymerase chain reaction or microarrays (72, 118); or cytokine-induced protein production (72). It is also helpful to demonstrate that cell-intrinsic function, i.e., the ability to respond to and produce the cytokine in question, is intact in the absence of the anticytokine autoantibody–containing autologous plasma.

TREATMENT

Therapy for anticytokine autoantibody–associated diseases has targeted both the consequences of the autoantibodies and the pathogenic autoantibody. For example, therapeutic whole-lung lavage repeatedly introduces and evacuates saline into each lung, thus flushing the accumulated proteinaceous alveolar material from the alveoli of patients with PAP (42). Patients with anticytokine autoantibody–associated infection receive targeted antimicrobials such as topical or systemic antifungals for mucocutaneous candidiasis with anti-IL-17A autoantibodies or antimycobacterials for NTM with anti-IFN-γ autoantibodies (66, 67, 72). Because these strategies do not influence the underlying immune mechanism, patients often require frequent or prolonged treatment.

In severe cases, a range of strategies have been employed to target the pathogenic autoantibody. PAP and disseminated NTM associated with anti-IFN-γ autoantibodies have been treated with exogenous GM-CSF (57, 58) and IFN-γ (72), respectively. Clinical improvement has been reported, although autoantibody levels after therapy were not routinely evaluated. One report of GM-CSF administration in PAP was associated with a reduction in plasma and bronchoalveolar lavage concentrations of anti-GM-CSF autoantibodies, suggesting induction of immune tolerance as a possible mechanism (140). Plasmapheresis and cyclophosphamide along with antimycobacterials were applied to one patient with anti-IFN-γ autoantibodies (68).

Rituximab, the mouse-human chimeric monoclonal antibody that targets the human B cell marker CD20, is approved for treatment of B cell lymphoma and RA. Because B cells ultimately differentiate into antibody-producing cells, rituximab has been used in a number of diseases caused by autoantibodies such as MG (141) and pemphigus vulgaris (a blistering skin disease caused by autoantibodies directed at the antikeratinocyte cell-surface protein, desmoglein 3) (142) with encouraging results. Successful rituximab therapy has also been reported in PAP (60) and anti-IFN-γ autoantibody–associated immunodeficiency (69) with reduction of autoantibody titers, yielding promising clinical results.

A new approach in PRCA is to bypass the autoantibody with an EPO receptor synthetic peptide agonist (hematide-Affymax) that does not share homology with the EPO ligand (143). Of the 14 patients studied, 13 had improvement in hemoglobin levels. Interestingly, the patient who failed therapy developed autoantibodies to the peptide as well. Although this strategy has not been applied to other anticytokine autoantibody–associated syndromes, it emphasizes how knowledge of the underlying disease mechanism can facilitate innovative therapeutic approaches.

CONCLUSIONS

Anticytokine autoantibodies can have severe consequences as well as highly varied manifestations. The phenotypes are not always those of infection, as in the case of PAP, anti-EPO-associated PRCA (21, 144), or severe osteoporosis associated with anti-osteoprotegerin autoantibodies in celiac disease (145). Their diagnosis, however, is critical because it can directly impact clinical management. The identification of anti-GM-CSF autoantibodies as the predominant cause of PAP (33, 34) came 40 years after the initial description of the disease (27), suggesting that current idiopathic diseases may someday be defined through identification of anticytokine autoantibodies. Furthermore, it was not intuitive that systemic autoantibodies to a hematopoietic growth factor would lead to lung disease until the identification of GM-CSF and GM-CSFR knockout mouse models (28, 29). The occurrence of autoantibodies to IL-17 and IL-22 in APECED, which results in CMC and is a hallmark of the disease, implicates anticytokine autoantibodies as an epigenetic consequence of genetic disease (146). The broad range of autoantibodies to receptors, as seen in diseases such as MG or Grave's disease, shows that anticytokine receptor autoantibodies, either stimulatory or inhibitory (147), could similarly be identified as pathogenic. Anticytokine autoantibodies are being increasingly recognized as agents central to the diagnosis and management of certain diseases. Beyond their potential to influence human biology, ranging from disease pathogenesis to immune homeostasis, they can offer fascinating windows onto fundamental mechanisms of immunity, inflammation, and infection.

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