Published in final edited form as:

Curr Opin Allergy Clin Immunol. 2010 December ; 10(6): 534–541. doi:10.1097/ACI.0b013e3283402b41.

Immunodeficiency secondary to anti-cytokine autoantibodies

Sarah K. Browne, MD and Steven M. Holland, MD

Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose of review—Anti-cytokine autoantibodies are an important and emerging mechanism of disease pathogenesis. We will review the clinical and laboratory features of syndromes in which immunodeficiency is caused by or associated with neutralizing anti-cytokine autoantibodies.

Recent findings—A growing number of patients have been described who demonstrate unique infectious phenotypes associated with neutralizing autoantibodies that target a particular cytokine known to participate in host defense against the offending organism.

Examples include—anti-granulocyte macrophage-colony stimulating factor (GM-CSF) autoantibodies and pulmonary alveolar proteinosis; anti-interferon(IFN)- γ autoantibodies and disseminated nontuberculous mycobacteria (NTM); anti-(interleukin)IL-6 autoantibodies and severe staphylococcal skin infection; anti-IL-17A, antiIL-17F or anti-IL-22 autoantibodies in patients with mucocutaneous candidiasis in the setting of both the autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) syndrome and in cases of thymoma.

Summary—Anti-cytokine autoantibodies have manifestations that are diverse, ranging from asymptomatic to life-threatening. These emerging and fascinating causes of acquired immunodeficiency may explain some previously idiopathic syndromes.

Keywords

Anti-cytokine autoantibodies; immunodeficiency; opportunistic infection

Introduction

Anti-cytokine autoantibodies are increasing as important mechanisms of disease pathogenesis. Their manifestations are diverse but they are often caused by a single polyclonal anti-cytokine IgG autoantibody. Examples include pulmonary alveolar proteinosis (PAP), due to anti-granulocyte macrophage colony stimulating factor (GM-CSF) autoantibodies; disseminated nontuberculous mycobacterial (NTM) disease due to anti-interferon(IFN)- γ autoantibodies; and pure red-cell aplasia (PRCA) due to anti-erythropoietin (EPO) autoantibodies. Anti-EPO antibodies do not result in immunodeficiency, but anti-IFN- γ autoantibodies may cause severe immunodeficiency. Although anti-GM-CSF autoantibodies, when causing disease, primarily result in severe and

Corresponding: Sarah K. Browne, MD CRC B3-4209 MSC 1684 Bethesda, MD 20892-1684 301-443-5806 voice 301-480-4506 faxbrownesa@niaid.nih.gov .

There are no conflicts of interest to disclose.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

chronic lung disease due to PAP, case reports indicate that some patients with PAP have unusual pulmonary and extrapulmonary infections, correlated with *in vitro* evidence that their antibodies cause both macrophage and granulocyte dysfunction[1,2]. Finally, other diseases such as autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) syndrome and thymoma [3**,4**] demonstrate high-titer neutralizing autoantibodies against multiple cytokines that may be acting in concert to impair host defense, although their direct role in disease causation remains to be definitively established.

While primary congenital immunodeficiencies tend to present early in life, anti-cytokine autoantibody syndromes tend to present in adulthood as a milder phenocopy of the congenital form, effecting a natural history that may wax and wane, depending on dynamic processes such as antibody titer or avidity. Given the accumulation of reports of new pathologic autoantibodies such as anti-osteoprotegerin autoantibodies associated with severe osteoporosis[5*] in some patients with celiac disease [5] and anti-IL-17 or anti-IL-22 autoantibodies associated with some chronic mucocutaneous candidiasis(CMC)[3,4] and practically boundless number of both endogenous soluble factors and clinical manifestations, there are likely to be many important anti-cytokine autoantibodies awaiting identification.

Text of Review

We will describe recent reports of anti-cytokine autoantibodies with particular focus on those that cause immunodeficiency (table 1) [6-22]. These reports identify individuals with an inappropriate production of specific (or possibly multiple) high-titer, neutralizing autoantibodies which, by blocking a given cytokine signalling pathway, can explain a particular clinical syndrome. Using other recent examples of anticytokine autoantibodies (which may or may not be associated with infectious complications) we hope to illustrate not only the complexity of anti-cytokine autoantibody phenomena but also how a better understanding of them lends itself to developing new treatments and gaining a deeper understanding of infection and inflammation (figure 1).

Anti-interferon- γ autoantibodies and disseminated nontuberculous mycobacterial infection

IFN γ is elaborated predominantly by activated T helper 1(T_H1) cells and is central to host defense against mycobacteria and other intracellular pathogens. It signals via the IFN- γ receptor (IFN- γ R), located primarily on monocytes and leads to phosphorylation and activation of downstream signaling molecules such as signal transducer and activator of transcription (STAT)1. STAT1 becomes phosphorylated and homodimerizes then translocates to the nucleus and initiates transcription of IFN- γ responsive genes that facilitate macrophage differentiation and elaboration of inflammatory mediators including TNF- α and IL-12. Susceptibility to tuberculosis (MTB) and nontuberculous mycobacterial (NTM) infection as well as listeriosis, salmonellosis, histoplasmosis, coccidioidomycosis, melioidosis, and penicilliosis has been demonstrated in patients with IFN- γ R deficiency (reviewed by Dorman et al.[16]). Other defects impacting the same metabolic pathway have similar susceptibilities, including STAT1, IL-12p40, IL-12Rb1, and NEMO[16]. The first cases of immunodeficiency caused by autoantibodies to IFN- γ were described in 2004[17,18].

There are now 14 HIV-negative adults reported with severe opportunistic infections in conjunction with high-titer neutralizing autoantibodies to IFN- γ [17-22*]. *In vitro*, anti-IFN- γ autoantibodies block downstream mediators of IFN- γ including STAT1 phosphorylation, TNF- α and IL-12 production, and IFN- γ responsive gene expression, suggesting that these autoantibodies interfere with the natural inflammatory response to infection with

mycobacteria. Clinically, all patients had at least one NTM infection and 5 were infected with multiple mycobacterial species. The most common organisms were *M. avium* complex (MAC) (11 infections) followed by rapid-growing mycobacteria (6 infections). Of the 14 reported cases, 11 were Asian suggesting possible genetic associations. Outcomes ranged from fatal infection to complete recovery.

Immunodeficiency caused by anti-IFN- γ autoantibodies is probably under-appreciated. Case series from Thailand and Taiwan have described HIV-negative patients with disseminated NTM[23,24], many of whom have high titer autoantibodies to IFN- γ (unpublished data).

Autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF)

The GM-CSF receptor is on many cell lineages, including neutrophils, macrophage precursors, dendritic cells, and megakaryocytes, where it mediates proliferation, differentiation, and immune activation. In both humans and mice GM-CSF influences terminal differentiation of monocytes to alveolar macrophages and augments innate immunity, largely through GM-CSF stimulation of the transcription factor PU.1[25-27].

GM-CSF and its receptor play critical roles in the pathogenesis of PAP. There are 3 distinct forms of PAP, each demonstrating abnormalities of surfactant metabolism that result in accumulation of acellular periodic acid-Schiff (PAS) positive proteinaceous material in pulmonary alveoli and development of large foamy, monocyte-like alveolar macrophages (reviewed by Trapnell et al.[2]). Primary PAP, the most severe form, results from mutations in the GM-CSF receptor and generally leads to respiratory failure and death shortly after birth[28]. Secondary PAP is often related to hematologic malignancies, iatrogenic immunosuppression or inhaled toxins, and results from qualitative or quantitative deficiency of alveolar macrophages[29]. The acquired form of PAP, first described in 1958 [30], was termed “idiopathic” PAP until anti-GM-CSF autoantibodies were identified as the cause nearly 40 years later[31,32].

Anti-GM-CSF autoantibodies in patients with PAP contribute to a range of defects in alveolar macrophage function including chemotaxis, adhesion, phagocytosis, microbicidal activity, and phagolysosome fusion[33,34]. Evidence from GM-CSF receptor-deficient mice suggests that GM-CSF induces PU.1, a gene critical to both surfactant homeostasis and TLR signaling [27], which potentially explains both surfactant accumulation and infection susceptibility seen in PAP. Defects have also been shown in neutrophil phagocytosis, adhesion, oxidative burst and bacterial killing from both PAP patient blood and from GM-CSF^{-/-} mouse bone marrow [1]. Anti-GM-CSF autoantibodies have been found not only in bronchoalveolar lavage material but also in the serum of patients with PAP[35], implying that the immune defects associated with this disease may extend beyond the lung. The reports of respiratory infections and extrapulmonary infections in PAP appear to exceed the expected hazards of underlying lung disease. The preponderance of infections in PAP for which neutrophils and macrophages are important mediators of host defense suggests an immune consequence for these anti-GM-CSF autoantibodies. Selected reports include pulmonary and CNS *Nocardia*[30,36-38], nocardia septic arthritis[39] and perinephric abscess[40]; disseminated histoplasmosis[41]; and disseminated cryptococcus[30,42]. Although some cases have been reported with pulmonary MAC, [43] none of these infections were treated with antimycobacterials and outcomes did not differ from those without infection. Unfortunately, the majority of these reports remain limited to case series and are further confounded by diagnostic heterogeneity, since most appeared prior to the knowledge that autoantibodies to GM-CSF were etiologic in the pathogenesis of PAP.

Anti-IL-17A, anti-IL-17F, or anti-IL-22 autoantibodies and chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) may complicate a multitude of disorders ranging from patients with congenital immunodeficiency to human immunodeficiency virus (HIV) to hematologic malignancy. CMC has recently been associated with anti-IL-17A, anti-IL-17F or anti-IL-22 autoantibodies in patients with the autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) syndrome[3,4]. APECED is a rare, autosomal recessive disorder caused by mutations in the autoimmune regulator (*AIRE*) gene that is characterized by a classic triad of CMC, hypoparathyroidism, and Addison's disease (reviewed by Perheentupa[44]). Although CMC in APECED has long been an enigma, CMC in other immunodeficiency syndromes has elucidated pathways which may be important to control these opportunists. Accordingly, *STAT3* deficient hyper IgE (Job's) syndrome[9,10], dectin-1 deficiency [11*], *CARD9* deficiency [12*], and to a lesser extent IL-12 receptor beta 1 deficiency[9] all have CMC and varying degrees of Th17 impairment, implicating this pathway in mucosal defense against *Candida*. Thus, the identification of anti-IL-17 anti-IL-17A, IL-17F or IL-22 autoantibodies in the vast majority of nearly 200 APECED indicates a novel group of pathogenic anti-cytokine autoantibodies that explain CMC in APECED.

Puel et al. evaluated 33 APECED patients and identified anti-IL17 autoantibodies in all 33 APECED patients tested, 29 of whom had CMC; healthy controls had neither those autoantibodies nor CMC [4]. They confirmed function of the anti-IL-17A antibody by inhibiting IL-6 production from IL-17 responsive fibroblasts. In another report, Kisand et al. examined 162 APECED patients and found anti-IL-17 A, IL-17F, and IL-22 autoantibodies in up to 90% of cases, also strongly associated with CMC [3]. They also identified anti-IL-17 and anti-IL-22 autoantibodies in two patients with thymoma and CMC, but none of 33 thymoma patients without CMC. Both groups report a few instances of autoantibodies without CMC, and there are many instances of CMC outside of APECED without autoantibodies. Furthermore, isolated PBMC of patients with CMC demonstrated significantly decreased IL-17-F and IL-22, with a trend towards decreased IL-17A production when stimulated with SEB or heat-killed *Candida* compared with controls [3]. Together, these data suggest that autoantibodies to IL-17 and IL-22 do not fully explain CMC. Nevertheless, the new work highlighting the roles of autoantibodies to IL-17 and IL-22 in CMC in APECED are a strong start towards developing new insight into the relationship between anti-cytokine autoantibodies and CMC.

APECED offers an enticing opportunity to study anti-cytokine autoantibodies because it is a fully penetrant Mendelian disorder with an identified gene defect. The defective gene in APECED, *AIRE*, promotes thymic expression of tissue-specific genes and permits intrathymic destruction of autoreactive T cells, thereby promoting survival of only self-tolerant T cells[45]. Autoantibodies in APECED were first described in a series of 76 APECED patients who all had neutralizing IgG autoantibodies to IFN α [46]. Although clearly biologically active *in vitro*, the physiologic consequences of these anti-IFN α autoantibodies are unclear. However, other autoantibodies in APECED are clearly pathologic, such as those to glutamic acid decarboxylase, thyroid peroxidase, 21-hydroxylase and now perhaps anti-IL-17A, IL-17F and IL-22. APECED embodies an exciting convergence of three fascinating and interrelated topics: CMC, immunodeficiency, and the origins of anti-cytokine autoantibodies.

Thymoma, autoantibodies and immunodeficiency

The thymus plays a critical role in T cell development, including negative selection of autoreactive T cells. Disruption of this process is seen with thymoma, an epithelial neoplasm

of the thymic cortex, and likely explains the link between thymoma and autoimmunity. Pathogenic autoantibodies are common in thymoma, most often in the form of myasthenia gravis caused by anti-acetylcholine receptor antibodies. Also described are a wide range of anti-cytokine autoantibodies, most commonly including IL-12 p35 and p40 subunits and type I interferons, but also other neutralizing anti-cytokine autoantibodies including those to IL-1 α , IL-17A, IL-22 [47]. Lack of *AIRE* expression has been shown in thymoma tissue[48,49] suggesting that beyond APECED, *AIRE* may play a role in other autoimmune conditions and, in particular, contribute to the development of anti-cytokine autoantibodies, which are striking features of both APECED and thymoma (figure 2).

While it is clear that a many anti-cytokine autoantibodies are elaborated in thymoma patients, no specific syndrome of immunodeficiency had been etiologically linked with these autoantibodies. Recently, we reported 17 patients with thymic neoplasm who were profiled for immunologic status, opportunistic infections and the presence of anti-cytokine autoantibodies [47*]. Five of 17 thymoma patients had opportunistic infections, all of whom had at least 3 anti-cytokine autoantibodies (range 3-11 of 39 cytokines screened). Interestingly, none of these patients met criteria for Good's syndrome, (thymoma, hypogammaglobulinemia and variable lymphopenia [50]). Infections ranged from CMC (3 patients), all with either IL-17A and/or IL-22 autoantibodies, confirming the previous report of these antibodies in thymoma with CMC [3], disseminated cryptococcosis (1 patient), sinopulmonary *M. avium* and *Scedosporium apiospermum* (1 patient), and disseminated varicella (2 patients). The patient with the most opportunistic infections (CMC, *M. avium* and *S. apiospermum*) also had the most anti-cytokine autoantibodies (11 of 39 screened). Although pulmonary alveolar proteinosis, and mycobacterial disease from anti-IFN- γ autoantibodies [19,20] demonstrate a clear relationship between a single autoantibody and a specific syndrome, the spectrum of infections identified in thymic neoplasm suggests that combinations of different autoantibodies may contribute to unique patterns of susceptibility. Since patients with opportunistic infections had higher numbers of autoantibodies, it is plausible that combinations of autoantibodies may have additive or synergistic effects.

Autoantibodies to interleukin-6

IL-6 is produced by a multitude of cells including lymphocytes, macrophages, and hepatocytes and is involved in both acute and chronic inflammation. In particular, IL-6 regulates the acute phase response in the liver, inducing production of C-reactive protein and other inflammatory markers. One case of neutralizing anti-IL-6 autoantibodies has been described in a Haitian boy who had two episodes of severe staphylococcal cellulitis and subcutaneous abscesses that complicated skin lesions initially caused by chickenpox and then mosquito bites[9]. Hyper-IgE syndrome, characterized by recurrent staphylococcal skin abscesses, is due to mutations in *STAT3*, the critical signal transduction molecule for IL-6 and IL-10 responses [7]. Undetectable C-reactive protein in the patient's blood, despite severe infection, further suggested an impaired response to IL-6[51]. His infections resolved without any apparent change in his anti-IL-6 autoantibody titers.

Autoantibodies to granulocyte colony-stimulating factor (G-CSF) in autoimmune disease

Granulocyte colony-stimulating factor is produced by bone marrow stromal cells at a low basal rate that can dramatically increase with physiologic stress, such as bacterial infection, or low absolute neutrophil counts[52]. It acts primarily on myeloid cells to accelerate maturation rate, increase neutrophil turnout from the bone marrow, and decrease constitutive neutrophil apoptosis. Beyond an important role in innate immunity, neutrophils may contribute to tissue destruction and inflammation seen in some autoimmune diseases [53].

Anti-G-CSF autoantibodies were identified in patients with Felty's syndrome (FS) (the clinical triad of rheumatoid arthritis, splenomegaly and neutropenia) and patients with SLE but not in patients with rheumatoid arthritis alone[6]. Eleven/16 patients studied with FS had anti-G-CSF autoantibodies; some patients with SLE had anti-G-CSF autoantibodies with either neutropenia or normal neutrophil levels. Three of 9 anti-G-CSF-containing plasmas tested inhibited G-CSF stimulated cell proliferation while the others did not, suggesting that there are different mechanisms of neutropenia in these patients or that the G-CSF autoantibodies are not the cause of the neutropenia. Although patients with FS may develop infections as a consequence of neutropenia[54,55], the authors did not evaluate the contribution of G-CSF autoantibodies to infection susceptibility.

Conclusion

Autoantibodies to cytokines can have severe consequences, as seen with autoantibodies to IFN- γ , GM-CSF or EPO. In PAP, the identification of anti-GM-CSF autoantibodies came over 40 years after the initial description of the syndrome suggesting that currently "idiopathic" diseases may someday be explained by neutralizing or agonizing autoantibodies.

Identification of anti-cytokine autoantibodies is critical because it will have important implications for the treatment of those diseases, with strategies to reduce autoantibody levels[56*], overcome the autoantibodies or induce tolerance with pharmacologic dosing of the inhibited cytokine[2,9], or use agents that bypass the cytokine which is inhibited. For example, a new approach the treatment of pure red-cell aplasia (anti-erythropoietin autoantibodies) is to bypass the autoantibody with a EPO receptor synthetic peptide agonist (hematide-Affymax) that does not share homology with the EPO ligand[57**]. In a series of patients treated with this agent, thirteen of the 14 patients studied had improvement in hemoglobin levels. Others have reported efforts to reduce autoantibody titers using plasmapheresis and cyclophosphamide [56] or rituximab [58*].

Autoantibodies to receptors, as seen in diseases such as myasthenia gravis or Grave's disease, suggest that immunodeficiency could be caused by anti-cytokine receptor autoantibodies. Autoantibodies may be inhibitory or stimulatory, may inhibit inflammatory or anti-inflammatory molecules, or may act in concert with other autoantibodies, providing countless possibilities for disease. The emerging role of anticytokine autoantibodies in disease pathogenesis offers a fascinating window onto the biology of immunity, inflammation and infection.

Acknowledgments

This work was supported by the Division of Intramural Research, NIAID, NIH.

References

1. Uchida K, Beck DC, Yamamoto T, Berclaz PY, Abe S, Staudt MK, Carey BC, Filippi MD, Wert SE, Denson LA, et al. GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. *N Engl J Med*. 2007; 356:567–579. [PubMed: 17287477]
2. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med*. 2003; 349:2527–2539. [PubMed: 14695413]
- 3 **. Kisand K, Wolff AS Boe, Podkrajsek KT, Tserel L, Link M, Kisand KV, Ersvaer E, Perheentupa J, Erichsen MM, Bratanic N, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med*. 2010; 207:299–308. [PubMed: 20123959] This was one of the first 2 papers identifying anti-IL-17A, IL-17F and

and IL-22 autoantibodies in strong association with candidiasis seen in APECED syndrome and in 2 patients with thymoma and CMC.

- 4 *. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, Cobat A, Ouachee-Chardin M, Toulon A, Bustamante J, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med*. 2010; 207:291–297. [PubMed: 20123958] This was one of the first 2 papers identifying anti-IL-17A, IL-17F and and IL-22 autoantibodies in strong association with candidiasis seen in APECED syndrome
- 5 *. Riches PL, McRorie E, Fraser WD, Determann C, van't Hof R, Ralston SH. Osteoporosis associated with neutralizing autoantibodies against osteoprotegerin. *N Engl J Med*. 2009; 361:1459–1465. [PubMed: 19812402] This paper is the first report of severe osteoporosis associated with anti-osteoprotegerin autoantibodies in celiac disease. It underscores the diverse range of phenotypes that may be caused by autoantibodies to endogenous factors.
6. Hellmich B, Csernok E, Schatz H, Gross WL, Schnabel A. Autoantibodies against granulocyte colony-stimulating factor in Felty's syndrome and neutropenic systemic lupus erythematosus. *Arthritis Rheum*. 2002; 46:2384–2391. [PubMed: 12355486]
7. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007; 357:1608–1619. [PubMed: 17881745]
8. Puel A, Picard C, Lorrot M, Pons C, Chrabieh M, Lorenzo L, Mamani-Matsuda M, Jouanguy E, Gendrel D, Casanova JL. Recurrent staphylococcal cellulitis and subcutaneous abscesses in a child with autoantibodies against IL-6. *J Immunol*. 2008; 180:647–654. [PubMed: 18097067]
9. de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, Feinberg J, von Bernuth H, Samarina A, Janniere L, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. *J Exp Med*. 2008; 205:1543–1550. [PubMed: 18591412]
10. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008; 452:773–776. [PubMed: 18337720]
- 11 *. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spruel AB, Venselaar H, Elbers CC, Johnson MD, Cambi A, Huysamen C, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. *N Engl J Med*. 2009; 361:1760–1767. [PubMed: 19864674] This paper represents a body of increasing evidence that the Th17 pathway is an important mediator of defense against *Candida* species.
- 12 *. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, Pfeifer D, Veelken H, Warnatz K, Tahami F, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009; 361:1727–1735. [PubMed: 19864672] This paper represents a body of increasing evidence that the Th17 pathway is an important mediator of defense against *Candida* species.
13. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med*. 2006; 203:2271–2279. [PubMed: 16982811]
- 14 *. Aujla SJ, Kolls JK. IL-22: a critical mediator in mucosal host defense. *J Mol Med*. 2009; 87:451–454. [PubMed: 19219418] This paper implicates IL-22 in mucosal defense and hence indirectly supports the hypothesis that anti-IL-22 autoantibodies seen in APECED and thymoma may be related to the development of CMC in these populations.
15. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. *Immunity*. 2004; 21:241–254. [PubMed: 15308104]
16. Dorman SE, Holland SM. Interferon-gamma and interleukin-12 pathway defects and human disease. *Cytokine Growth Factor Rev*. 2000; 11:321–333. [PubMed: 10959079]
17. Doffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S, Ceron-Gutierrez L, Espitia-Pinzon C, Barnes N, Bothamley G, Casanova JL, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. *Clin Infect Dis*. 2004; 38:e10–14. [PubMed: 14679469]

18. Hoflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Docke WD, Grutz G, Meisel C, Halle E, Gobel UB, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with *Mycobacterium chelonae* and *Burkholderia cenocepacia*. *Blood*. 2004; 103:673–675. [PubMed: 12947000]
19. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, Nicol M, Scholvinck E, Relman D, Waddell S, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-gamma. *J Clin Invest*. 2005; 115:2480–2488. [PubMed: 16127458]
20. Patel SY, Ding L, Brown MR, Lantz L, Gay T, Cohen S, Martyak LA, Kubak B, Holland SM. Anti-IFN-gamma autoantibodies in disseminated nontuberculous mycobacterial infections. *J Immunol*. 2005; 175:4769–4776. [PubMed: 16177125]
21. Tanaka Y, Hori T, Ito K, Fujita T, Ishikawa T, Uchiyama T. Disseminated *Mycobacterium avium* complex infection in a patient with autoantibody to interferon-gamma. *Intern Med*. 2007; 46:1005–1009. [PubMed: 17603241]
- 22 *. Koya T, Tsubata C, Kagamu H, Koyama K, Hayashi M, Kuwabara K, Itoh T, Tanabe Y, Takada T, Gejyo F. Anti-interferon-gamma autoantibody in a patient with disseminated *Mycobacterium avium* complex. *J Infect Chemother*. 2009; 15:118–122. [PubMed: 19396523] This is another of a growing number of adult HIV-negative Asian patients with severe disseminated nontuberculous mycobacterial infection in clear association with anti-IFN- γ autoantibodies.
23. Chetchotisakd P, Kiertiburanakul S, Mootsikapun P, Assanasen S, Chaiwarith R, Anunnatsiri S. Disseminated nontuberculous mycobacterial infection in patients who are not infected with HIV in Thailand. *Clin Infect Dis*. 2007; 45:421–427. [PubMed: 17638188]
24. Lai CC, Lee LN, Ding LW, Yu CJ, Hsueh PR, Yang PC. Emergence of disseminated infections due to nontuberculous mycobacteria in non-HIV-infected patients, including immunocompetent and immunocompromised patients in a university hospital in Taiwan. *J Infect*. 2006; 53:77–84. [PubMed: 16313964]
25. Bonfield TL, Raychaudhuri B, Malur A, Abraham S, Trapnell BC, Kavuru MS, Thomassen MJ. PU.1 regulation of human alveolar macrophage differentiation requires granulocyte-macrophage colony-stimulating factor. *Am J Physiol Lung Cell Mol Physiol*. 2003; 285:L1132–L1136. [PubMed: 12896880]
26. Chen BD, Mueller M, Chou TH. Role of granulocyte/macrophage colony-stimulating factor in the regulation of murine alveolar macrophage proliferation and differentiation. *J Immunol*. 1988; 141:139–144. [PubMed: 3288696]
27. Shibata Y, Berclaz PY, Chronoes ZC, Yoshida M, Whitsett JA, Trapnell BC. GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. *Immunity*. 2001; 15:557–567. [PubMed: 11672538]
28. Carey B, Trapnell BC. The molecular basis of pulmonary alveolar proteinosis. *Clin Immunol*. 2010; 135:223–35. [PubMed: 20338813]
29. Ladeb S, Fleury-Feith J, Escudier E, Van Nhieu J Tran, Bernaudin JF, Cordonnier C. Secondary alveolar proteinosis in cancer patients. *Support Care Cancer*. 1996; 4:420–426. [PubMed: 8961472]
30. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. *N Engl J Med*. 1958; 258:1123–1142. [PubMed: 13552931]
31. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, Nakata K. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. *J Exp Med*. 1999; 190:875–880. [PubMed: 10499925]
32. Uchida K, Nakata K, Trapnell BC, Terakawa T, Hamano E, Mikami A, Matsushita I, Seymour JF, Oh-Eda M, Ishige I, et al. High-affinity autoantibodies specifically eliminate granulocyte-macrophage colony-stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. *Blood*. 2004; 103:1089–1098. [PubMed: 14512323]
33. Golde DW, Territo M, Finley TN, Cline MJ. Defective lung macrophages in pulmonary alveolar proteinosis. *Ann Intern Med*. 1976; 85:304–309. [PubMed: 183578]
34. Gonzalez-Rothi RJ, Harris JO. Pulmonary alveolar proteinosis. Further evaluation of abnormal alveolar macrophages. *Chest*. 1986; 90:656–661. [PubMed: 3769565]

35. Kitamura T, Uchida K, Tanaka N, Tsuchiya T, Watanabe J, Yamada Y, Hanaoka K, Seymour JF, Schoch OD, Doyle I, et al. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. *Am J Respir Crit Care Med*. 2000; 162:658–662. [PubMed: 10934102]
36. Fried J, Hinthorn D, Ralstin J, Gerjarusak P, Liu C. Cure of brain abscess caused by *Nocardia asteroides* resistant to multiple antibiotics. *South Med J*. 1988; 81:412–413. [PubMed: 3279539]
37. Walker DA, McMahon SM. Pulmonary alveolar proteinosis complicated by cerebral abscess: report of a case. *J Am Osteopath Assoc*. 1986; 86:447–450. [PubMed: 3528083]
38. Oerlemans WG, Jansen EN, Prevo RL, Eijsvogel MM. Primary cerebellar nocardiosis and alveolar proteinosis. *Acta Neurol Scand*. 1998; 97:138–141. [PubMed: 9517865]
39. Clague HW, Harth M, Hellyer D, Morgan WK. Septic arthritis due to *Nocardia asteroides* in association with pulmonary alveolar proteinosis. *J Rheumatol*. 1982; 9:469–472. [PubMed: 7120244]
40. Andersen BR, Ecklund RE, Kellow WF. Pulmonary alveolar proteinosis with systemic nocardiosis. A case report. *Jama*. 1960; 174:28–31. [PubMed: 13793307]
41. Hartung M, Salfelder K. Pulmonary alveolar proteinosis and histoplasmosis: report of three cases. *Virchows Arch A Pathol Anat Histol*. 1975; 368:281–287. [PubMed: 813367]
42. Sunderland WA, Campbell RA, Edwards MJ. Pulmonary alveolar proteinosis and pulmonary cryptococcosis in an adolescent boy. *J Pediatr*. 1972; 80:450–456. [PubMed: 5060458]
43. Witty LA, Tapson VF, Piantadosi CA. Isolation of mycobacteria in patients with pulmonary alveolar proteinosis. *Medicine (Baltimore)*. 1994; 73:103–109. [PubMed: 8152364]
44. Perheentupa J. APS-1/APECED: the clinical disease and therapy. *Endocrinol Metab Clin North Am*. 2002; 31:295–320. vi. [PubMed: 12092452]
45. Derbinski J, Schulte A, Kyewski B, Klein L. Promiscuous gene expression in medullary thymic epithelial cells mirrors the peripheral self. *Nat Immunol*. 2001; 2:1032–1039. [PubMed: 11600886]
46. Meager A, Visvalingam K, Peterson P, Moll K, Murumagi A, Krohn K, Eskelin P, Perheentupa J, Husebye E, Kadota Y, et al. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Med*. 2006; 3:e289. [PubMed: 16784312]
- 47 *. Burbelo PD, Browne SK, Sampaio EP, Giaccone G, Zaman R, Ervand K, Rajan A, Ding L, Ching KH, Berman A, et al. Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. *Blood*. 2010 epub ahead of print. This paper demonstrated a wide range of biologically active anti-cytokine autoantibodies in multiple patients associated with a high prevalence of opportunistic infection.
48. Offerhaus GJ, Schipper ME, Lazenby AJ, Montgomery E, Morsink FH, Bende RJ, Musler AR, van Lier RA, van Noesel CJ. Graft-versus-host-like disease complicating thymoma: lack of AIRE expression as a cause of non-hereditary autoimmunity? *Immunol Lett*. 2007; 114:31–37. [PubMed: 17928069]
49. Scarpino S, Di Napoli A, Stoppacciaro A, Antonelli M, Pillozzi E, Chiarle R, Palestro G, Marino M, Facciolo F, Rendina EA, et al. Expression of autoimmune regulator gene (AIRE) and T regulatory cells in human thymomas. *Clin Exp Immunol*. 2007; 149:504–512. [PubMed: 17590173]
50. Kelleher P, Misbah SA. What is Good's syndrome? Immunological abnormalities in patients with thymoma. *J Clin Pathol*. 2003; 56:12–16. [PubMed: 12499426]
51. Castell JV, Gomez-Lechon MJ, David M, Andus T, Geiger T, Trullenque R, Fabra R, Heinrich PC. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Lett*. 1989; 242:237–239. [PubMed: 2464504]
52. Watari K, Asano S, Shirafuji N, Kodo H, Ozawa K, Takaku F, Kamachi S. Serum granulocyte colony-stimulating factor levels in healthy volunteers and patients with various disorders as estimated by enzyme immunoassay. *Blood*. 1989; 73:117–122. [PubMed: 2462934]
53. Eyles JL, Roberts AW, Metcalf D, Wicks IP. Granulocyte colony-stimulating factor and neutrophils--forgotten mediators of inflammatory disease. *Nat Clin Pract Rheumatol*. 2006; 2:500–510. [PubMed: 16951705]

54. Campion G, Maddison PJ, Goulding N, James I, Ahern MJ, Watt I, Sansom D. The Felty syndrome: a case-matched study of clinical manifestations and outcome, serologic features, and immunogenetic associations. *Medicine (Baltimore)*. 1990; 69:69–80. [PubMed: 1969604]
55. Ruderman M, Miller LM, Pinals RS. Clinical and serologic observations on 27 patients with Felty's syndrome. *Arthritis Rheum*. 1968; 11:377–384. [PubMed: 5301597]
- 56 *. Baerlecken N, Jacobs R, Stoll M, Schmidt RE, Witte T. Recurrent, multifocal *Mycobacterium avium-intercellulare* infection in a patient with interferon-gamma autoantibody. *Clin Infect Dis*. 2009; 49:e76–78. [PubMed: 19725781] This paper reports a patient with anti-IFN- γ autoantibodies and dNTM who was treated with plasmapheresis and cyclophosphamide in an effort to target the pathogenic autoantibodies beyond treating the related infections with antimycobacterials.
- 57 **. Macdougall IC, Rossert J, Casadevall N, Stead RB, Duliege AM, Froissart M, Eckardt KU. A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N Engl J Med*. 2009; 361:1848–1855. [PubMed: 19890127] This paper suggests an exciting new strategy for treatment of diseases caused by autoantibodies. The agent was studied for the treatment of pure red-cell aplasia caused by anti-erythropoietin (EPO) autoantibodies and is a EPO receptor agonist that does not share homology with EPO, thus remaining unaffected by the presence of the neutralizing anti-EPO autoantibodies.
- 58 *. Borie R, Debray MP, Laine C, Aubier M, Crestani B. Rituximab therapy in autoimmune pulmonary alveolar proteinosis. *Eur Respir J*. 2009; 33:1503–1506. [PubMed: 19483052] This reports one patient with PAP who was treated with rituximab and demonstrated improved clinical status and decreased neutralizing activity of anti-GM-CSF autoantibodies.

Figure 1.
Examples of currently known anti-cytokine autoantibodies syndromes.

Figure 2. Relationship between overlapping genetics and phenotype identified in certain anti-cytokine autoantibody-associated syndromes.

Table 1

Clinical and biological evidence for contribution of anticytokine autoantibodies to disease pathogenesis

Cytokine target	Biological rational <i>in vivo</i>	Supporting evidence <i>in vitro</i>	Supporting evidence <i>in vivo</i>	Comments
G-CSF ^a	G-CSF critical for differentiation and expansion of neutrophils; autoantibodies associated with neutropenia in Felty's syndrome [6] ^c	IgG fraction of some of the patients with anti-G-CSF autoantibodies inhibited cell survival and proliferation in a G-CSF/IL ^b -3 dependent cell line [6]	Neutropenia	Associated with patients with Felty's syndrome and systemic lupus erythematosus
GM-CSF ^c	GM-CSF critical for differentiation of monocytes to alveolar macrophages which play important role in metabolism of surfactant. Hallmark of PAP ^d is accumulation of surfactant (reviewed by [2])	Serum from patients with PAP inhibits growth of GM-CSF dependent cell line; identified as neutralizing IgG autoantibody present in bronchoalveolar lavage fluid and serum	BAL fluid contains large foamy macrophages or monocyte-like macrophages and elevated levels of surfactant proteins	Pulmonary and extra-pulmonary infections with <i>Nocardia</i> , <i>Aspergillus</i> , <i>Proteus</i> , <i>Cryptococcus</i> and disseminated <i>Histoplasmosis</i> reported. Many of these reports are prior to known cause of PAP (anti-GM-CSF autoantibodies)
IL-6	IL-6 signaling mediated by STAT ^e -3 [7] and defects in STAT-3 result in severe staphylococcal skin infections; autoantibodies to IL-6 associated with recurrent staphylococcal skin infection [8]	Neutralizing IL-6 autoantibodies prevented STAT-3 phosphorylation and production of C-reactive protein (CRP) mRNA in Hep3B cell line [8]	Severe staphylococcal skin infection with undetectable CRP during episodes of severe infection with other markers of systemic inflammation (fever, elevated neutrophil count) [8]	Only one case reported to date
IL-17	Genetic diseases which resulting in susceptibility to <i>Candida</i> demonstrate impaired Th17 function [9,10,11*,12*]	Anti-IL-17A autoantibodies in APECED patients inhibited IL-17A-induced IL-6 production in human fibroblasts; no in-vitro assessment of biological activity of IL-17F antibodies	Patients with APECED syndrome and two patients with thymoma and CMC demonstrated neutralizing autoantibodies to IL-17A and/or IL-17F [3**,4**]	Some patients with these autoantibodies do not have CMC; others without these autoantibodies do have CMC
IL-22	IL-22, coexpressed in Th17 cells [13], plays a role in mucosal immunity [14*,15]	No assessment of biological activity of IL-22 autoantibodies	Patients with APECED syndrome and two patients with thymoma and CMC demonstrated neutralizing autoantibodies to IL-22 [3**,4**]	Some patients with these autoantibodies do not have CMC; others without these autoantibodies do have CMC
IFN ^g - γ	IFN- γ is critical for monocyte activation and host control of mycobacterial infections; defects in this pathway result in severe opportunistic infection with nontuberculous mycobacteria (NTM) [16]	Autoantibodies block IFN- γ -stimulated STAT-1 phosphorylation as well as IL-12 and TNF- α production by monocytes	High-titer highly neutralizing IgG anti-IFN- γ autoantibodies identified in patients with severe disseminated NTM infection and no other evidence of immunodeficiency [17–21,22*]	11 of 14 reported cases of Asian descent

^aGranulocyte-colony stimulating factor.^bIL, interleukin.^cGM-CSF, granulocyte macrophage-colony stimulating factor.^dPAP, pulmonary alveolar proteinosis.

^eSTAT, signal transducer and activator of transcription.

^fCMC, chronic mucocutaneous candidiasis.

^gIFN, Interferon.