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ANTI-CYTOKINE AUTOANTIBODIES: AUTOIMMUNITY TRESPASSING ON ANTIMICROBIAL IMMUNITY

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Abstract

Anti-cytokine autoantibodies (ACAAs) can cause immunodeficiency or dysregulate immune responses. They may phenocopy genetically defined primary immunodeficiencies. We review current anti-Type 1 and 2 interferon, anti-interleukin-12/23, anti-interleukin-17, anti-granulocyte-macrophage-colony-stimulating-factor autoantibodies, HLA associations, disease associations, and mechanistically based treatment options. Suspecting and identifying patients at the onset of symptoms should ameliorate disease and improve outcomes.

Keywords

anti-cytokine autoantibodies; anti-interferon-gamma; anti-interferon-alpha; anti-interleukin-23; anti-interleukin-12; anti-interleukin-17; anti-granulocyte-macrophage colony stimulating factor; opportunistic infections; adult-onset immunodeficiency; protein alveolar proteinosis; chronic mucocutaneous candidiasis

INTRODUCTION

High titer neutralizing anti-cytokine autoantibodies (ACAAs), typically polyclonal IgG, are increasingly recognized in diverse infectious and/or immunological conditions (1–3). Anti-interferon-gamma (IFN-γ) autoantibodies are seen in disseminated mycobacterial disease; anti-interleukin-17 (IL-17) in chronic mucocutaneous candidiasis (CMC); anti-granulocyte-macrophage-colony-stimulating-factor (GM-CSF) in cryptococcosis, nocardiosis and

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pulmonary alveolar proteinosis; anti-IL-6 in staphylococcal sepsis; and anti-Type I interferons in viral infections and severe COVID-19 (4–12).

ACAAs are common, even in healthy individuals (12, 13). They may affect cytokine biology by diminishing or augmenting signaling or by altering their half-life in the circulation (13–19). In contrast to pathogenic ACAAs associated with immunodeficiency, regulatory ACAAs are not as inhibitory, and are typically detected at lower binding titers (20, 21). With age, the frequency of ACAAs increases, and their respective titers and functionality may change in the setting of endogenous ligands, such as in ARDS and sepsis, or anti-Type 1 interferons during the onset of acute COVID19 (22, 23). The probability that ACAAs are deterministic (have an immunoregulatory function) rather than stochastic (appear independent of physiological effects) increases as their neutralizing activity increases.

Anti-interferon-γ autoantibodies

Interferon-γ is the key macrophage-activating factor secreted by αβ+ (including natural killer T (NKT), mucosal associated invariant T (MAIT) cells, conventional CD4+ and CD8+ T cells), γδ+ T cells, B cells, NK cells, and some innate lymphoid cells (ILCs) (24). Patients with neutralizing anti-IFN-γ autoantibodies (or any of the known inborn errors of IFN-γ due to defects in 16 distinct genes) are prone to mycobacterial disease and related infections by intra-macrophagic microbes (25, 26). Over 600 cases have been reported since the first fatal cases were described in 2004 (27–29). There is a preponderance of HIV-uninfected individuals of East Asian descent (including Filipino, Thai, Taiwanese, Laotian, Japanese, Chinese but not Koreans) with HLA-DRB1*15:02/16:02 and HLA-DQB1*05:01/05:02 (30, 31). However, recent reports in Caucasians, two children, a Surinamese individual of African descent, a Sri-Lankan man, and an HIV-positive individual with opportunistic infections years after immune reconstitution, suggest that this autoimmune phenomenon may be more widespread (32–36).

Lymph nodes, bones/joints, and lungs are most affected, with occasional soft tissue and skin involvement (in the form of reactive neutrophilic dermatosis, erythema nodosum, or exanthematous pustulosis) (37, 38). Lymph node histopathology may be mistaken for T-cell lymphoma (50% show monoclonality, 33% may be indistinguishable from angioimmunoblastic T-cell lymphoma by criteria), IgG4-related disease, or multicentric Castleman disease. These episodes of mimicry highlight the need to culture and stain for mycobacteria in the evaluation of lymphadenopathy or to at least consider anti-IFN-γ autoantibodies before chemotherapy or corticosteroids (39–41). The microbial spectrum includes *Salmonella*, *Burkholderia, Bacillus* species, *Cryptococcus*, *Talaromyces*, *Coccidioides, Histoplasma*, *Toxoplasma* and varicella-zoster, herpes simples and cytomegalovirus (4, 42–45).

Anti-IFN-γ autoantibodies block IFN-γ binding to its receptor and downstream phosphorylation of Signal Transducer and Activator of Transcription 1 (STAT1). Blockade of IFN-γ induced STAT1 phosphorylation by patient plasma or serum *in vitro* is the simplest assay for anti-IFN-γ autoantibodies (46, 47). However, one of the most common and clinically accessible tests is the QuantiFERON Gold In-Tube, which relies on detection of IFN-γ elaborated in response to antigen or mitogen; it is blocked by anti-IFN-γ

autoantibodies. Therefore, either a positive or a negative QuantiFERON Gold result indicate that IFN-γ produced in response to mitogen was detected and argue strongly against the presence of anti-IFN-γ autoantibodies; in contrast, an indeterminate result is consistent with anti-IFN-γ autoantibodies (48, 49).

Exogenous IFN-γ does not ameliorate disease since these autoantibodies are typically quite high titer (4, 50). In contrast, immunomodulation with cyclophosphamide, rituximab, bortezomib, abatacept and daratumumab have all been partially successful in severe or refractory cases (37, 51–55). These reports suggest that reducing autoantibody-producing B-cells or plasma cells may help control infections (56). However, not all cases require immune directed therapy and in many patients the levels of anti-IFN-γ autoantibodies declines over time in conjunction with treatment of the mycobacterial disease (38). The direction of the causality here is unresolved.

Anti-IL-12 and IL-23 autoantibodies

IL-12 and IL-23 share the p40 subunit and both use the IL12Rβ1 receptor and are essential for optimal production of IFN-γ (57, 58). Therefore, it is unsurprising that autoantibodies against them are also associated with opportunistic infections. Anti-IL12 and anti-IL23 autoantibodies are found in 33–45% of patients with thymoma overall, but in patients with recurrent sinopulmonary or disseminated infections, anti-IL12 and anti-IL23 frequencies increase to >95% (16, 59–61) and unpublished data).

Anti-GM-CSF autoantibodies

Cryptococcosis (particularly *C. gattii*) and nocardiosis may disseminate to the brain in seemingly immunocompetent individuals and have been associated with neutralizing **anti-GM-CSF** autoantibodies, which also cause autoimmune pulmonary alveolar proteinosis (aPAP)(62–66). Anti-GM-CSF-mediated disruption of STAT5 signaling and PU.1 nuclear translocation results in alveolar macrophage dysfunction, intra-alveolar accumulation of surfactant lipoproteinaceous material, and the insidious onset of interstitial lung disease (67, 68). Anti-GM-CSF autoantibodies are associated with HLA-DRB1*08:03 in Japanese patients with aPAP (69). Treatments for aPAP have included whole lung lavage, inhaled recombinant human GM-CSF, and rituximab (70–72). Anti-GM-CSF autoantibodies concentration are lower in bronchoalveolar lavage than in the blood, hence exogenous inhaled GM-CSF, unlike exogenous IFN-γ, may overcome some of the neutralizing activity at the site of tissue pathology (73). Rituximab is less effective against anti-GM-CSF autoantibodies than anti-IFN-γ autoantibodies, suggesting that anti-GM-CSF autoantibodies may be produced by long-lived plasma cells and memory B-cells which no longer express CD20 (74).

Anti-IL-17 autoantibodies

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) patients with biallelic mutations in *AIRE* and to a lesser degree, patients with thymic epithelial tumors, have been described to have neutralizing autoantibodies to T_h17 cytokines including IL17A/F, IL22, and Type 1 interferons (5, 6). Chronic mucocutaneous candidiasis (CMC), characterized by chronic, non-invasive *Candida* spp. infections of the skin, nails, and mucus

membranes is the most notable infectious manifestation in APECED patients, whereas in thymoma patients, CMC may be accompanied by recurrent sinopulmonary infections exacerbating bronchiectasis or overshadowed by disseminated infections associated with anti-IL12/23 autoantibodies or Good syndrome (61, 75). While these anti-IL17 autoantibodies phenocopy some of the primary immune defects (IL17F, IL17RA, IL17RF, ACT1), recent data have also shown excessive IFN-γ production by mucosal T cells to cause candidiasis in APECED (76). Therefore, the exact role of anti-IL-17 autoantibodies in APECED is still under investigation.

Anti-Type I interferon autoantibodies

Neutralizing autoantibodies against Type I IFNs have been associated with >10% of life-threatening COVID-19 cases in multiple cohorts, particularly in men over sixty (11, 77–79). These neutralizing anti-IFN-α and anti-IFN-ω autoantibodies are found in 4% of the population > 70 years, in 5–6% of patients with systemic lupus erythematosus, in 59–64 % of thymoma patients with myasthenia gravis, and in 100% of APECED patients (15, 22, 61, 80, 81). Clinical penetrance for severe COVID-19 is incomplete across these diverse populations with pre-existing anti-Type I interferon autoantibodies (82). Some APECED patients with high titer neutralizing anti-IFN-α and anti-IFN-ω autoantibodies who contracted SARS-CoV-2 have had only mild COVID-19, whereas in the general population, no individuals with mild COVID-19 had detectable anti-IFN-α and anti-IFN-ω autoantibodies (78, 83, 84). Anti-IFN-α and anti-IFN-ω autoantibodies in APECED patients are unchanged by COVID-19. In contrast, serial sampling during and after severe COVID-19 in otherwise normal people identified highly dynamic and declining levels of anti-IFN-α, sometimes to undetectable levels in convalescence (Elana Shaw, submitted). Neutralization of IFN-β-induced STAT1 phosphorylation *in vitro* was seen in only 2% of those with anti-IFN-α and anti-IFN-ω autoantibodies (11, 22, 84). Preemptive use of IFN-β in an individual with with incontinentia pigmenti and autoantibodies against IFN-α and IFN-ω was successful despite a high initial viral load of SARS-CoV-2 (85). Individualized approaches will be needed in those with chronic autoimmunity and multiple ACAAs, since some may have compensatory alterations in interacting cytokine pathways (85, 86). Outside of COVID-19, neutralizing Type 1 IFNs autoantibodies have been found when looked for in unusually severe viral illnesses (12, 87).

CONCLUSIONS

High throughput autoantibody screening will certainly identify new targets and new mechanisms of infectious and organ-specific diseases. We recommend screening for anti-interferons, anti-IL17, anti-GM-CSF and anti-IL23 in appropriate patients with otherwise unknown etiologies for opportunistic infections and/or in those with known autoimmunity, but more importantly, correlating binding specificities with appropriate functional assays. The clinical penetrance of ACAAs is incomplete, suggesting that these syndromes result from a combination of factors including environmental and genetic ones. It is imperative to consider ACAAs in the setting of unexplained or severe infections, as directed therapies may ameliorate their effects. These often silent and underappreciated modulators of severe infections are increasing in recognition and clinical importance.

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LIST OF ABBREVIATIONS (alphabetical)

ACAAs	anti-cytokine autoantibodies
aPAP	autoimmune protein alveolar proteinosis
APECED	autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
ARDS	adult respiratory distress syndrome
CMC	chronic mucocutaneous candidiasis
COVID19	coronavirus virus disease 2019
IFN-α	interferon-alpha
IFN-β	interferon-beta
IFN-γ	interferon-gamma
IFN-ω	interferon-omega
IL12	interleukin-12
IL17	interleukin-17
IL-22	interleukin-22
IL23	interleukin-23
GM-CSF	granulocyte-macrophage colony stimulating factor
STAT1	Signal Transducer and Activator of Transcription
STAT5	Signal Transducer and Activator of Transcription

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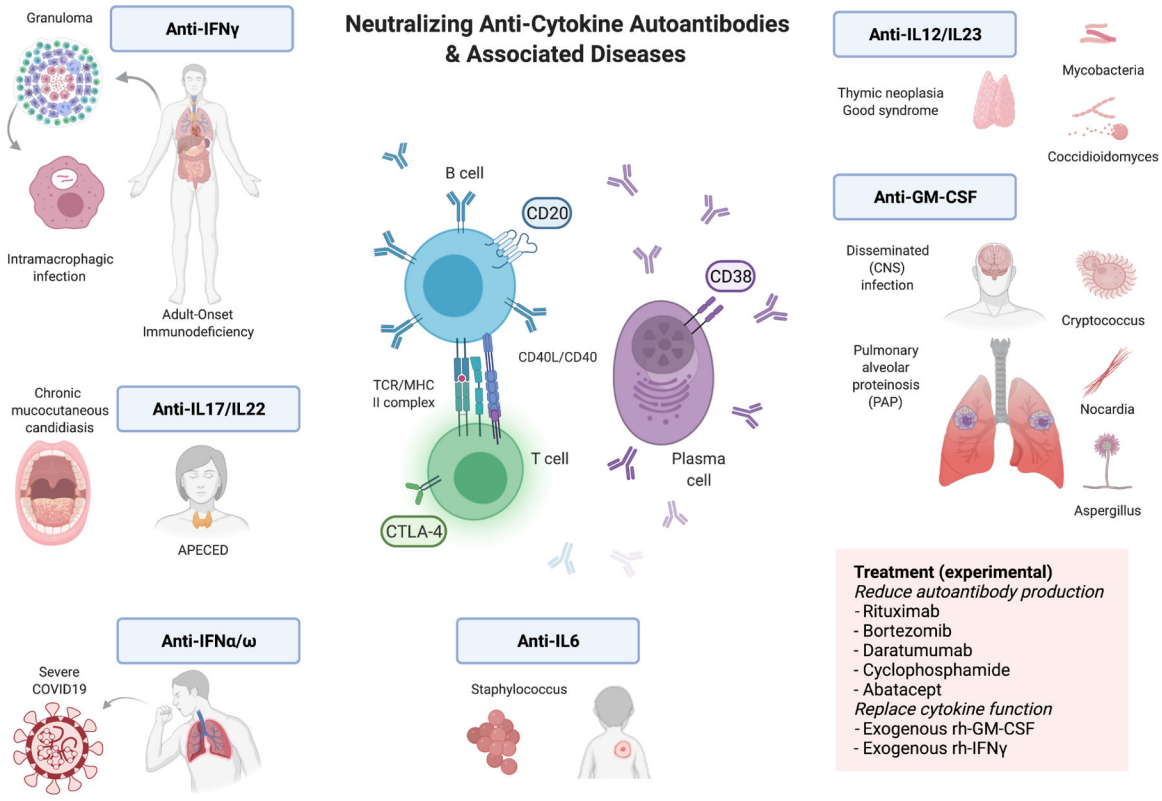

Figure 1:
Pictorial abstract of the disease associations and mechanistic-based therapy of anti-cytokine autoantibodies.