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Autoantibodies Against Cytokines: What do they Tell Us?

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ABSTRACT

Anti-cytokines autoantibodies (ACAA) are types of autoantibodies against soluble immune factors and may be mirrored by autoimmune disease biomarkers. The manifestation of secretion of these antibodies is associated to primary immunodeficiency (PID), but also directly or indirectly related to infectious disease occurrence, which could be assumed as a consequence of cytokine deficiency. These antibodies are of their mature antibody isotype and could exert functional humoral response against target cytokines. However, no immunoglobulin deficiency cases have been observed in association with ACAA secretion, and the function and secretion of ACAAs were not always correlated to pathogenesis. Therefore, the mechanisms underlining the presence of these antibodies remain poorly known and the findings are somehow debatable between studies. This review is trying to summarize the recent findings on clinical relevance of ACAAs and related pathologies to which an unneglectable fraction of autoantibodies are associated. Also, it is attempting to establish the missing connections of these autoantibodies found in several autoimmune or infectious diseases by proposing the possible mechanisms associated to primary immunodeficiency and genetic defect. At the end, we also try to rationalize how we could learn from these atypical antibodies and use them as prognosis biomarkers or therapeutic targets of different pathologies.

Keywords: Anti-Cytokines Autoantibodies; Autoimmune Disease; Infectious Disease; Primary Immunodeficiency

Abbreviations: ACAAs: Anti-Cytokine Autoantibodies; T1D: Type 1 Diabetes; IL: Interleukin; IFN: Interferons; MS: Multiple Sclerosis; SSc: Systemic Sclerosis; SLE: Systemic Lupus Erythematosus; RA: Rheumatoid Arthritis; PID: Primary Immunodeficiencies; ILD: Interstitial Lung Disease; IPEX: Immunodysregulation Polyendocrinopathy Enteropathy X-Linked; TNF: Tumor Necrosis Factor; PAD: Primary Antibody Deficiencies; CVID: Common Variable Immune Deficiency; SIgAD: Selective IgA Deficiency; OA: Osteoarthritis; ALPS: Lymphoproliferative Syndrome; APECED: Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy; BENTA Disease: B-Cell Expansion with NF-κB and T-Cell Anergy; CEDS: Caspase Eight Deficiency State; BCR: B-Cell Receptor; BAFF: B Cell Activation Factor; APRIL: A Proliferation-Inducing Ligand

Introduction

Cases of anti-cytokines autoantibodies (ACAAs) increasingly reported were firstly recorded in late 1980s [1-3]. Regardless the titer and the phenotypes, they were initially found in both healthy subjects and patients manifesting chronical inflammation, autoimmune diseases, in a highly variable and infrequent manner3. There are five families of cytokines: chemokines, interferons (IFNs), interleukins, lymphokines, and tumor necrosis factor (TNFs), and reported cases of ACAAs were shown against most of these families, but were not able to recognize all the existing cytokines. In addition, ACAAs were also reportedly found in different infectious diseases [4-7]. These infectious diseases may potentiate autoimmune disorders, or chronical inflammation, as consequences of ACAAs secretions that potentially neutralize the cytokine which we could call 'cytokine deficiency'. The correlation between ACAAs and pathologies was difficultly made due to their unproportionable titers. It was recently shown that primary immunodeficiency (PID) [1] which impacts different layers of immune system, including T cell and B cell dysfunctions, may play a pivotal role in triggering the secretions of these ACAAs [8-12]. Of note, these ACAAs are also of their mature phenotype, mostly immunoglobulin G (IgG), suggesting its full maturation status despite of primary immunodeficiency manifestation that may impact B cell functions on which the secretion of ACAAs depend [7,13,14]. Some of these ACAAs are potent, functional, and antigen specific, showed by *in vitro* neutralization assays, and of considerable titer compared to other autoantibodies and antibodies against pathogens. This mini review is approaching

1) The correlation between appearance of ACAAs and clinical consequences of autoimmune and infectious diseases;

2) The relevance between primary immunodeficiency and appearance of ACAAs;

3) The usefulness of using these ACAAs as prognosis biomarkers or pharmaceutical targets of immunotherapy.

Cases of ACAAs and Clinical Significances Related to Autoimmune Disorders

A list of autoimmune pathologies related to ACAA clinical implications were summarized in Table 1. The remarkable cases are for example, ACAA against IL-1α in rheumatoid arthritis (RA) patients [15-17] or against IFN-α and G-CSF in systemic lupus erythematosus (SLE) patients [18,19] and interferon autoantibodies in Sjogren's syndrome (SS) patients [20,21] but also those against TNF-α and IFN-γ in multiple sclerosis (MS) [22]. In some other autoimmune diseases, the symptoms are more diverse and implicate diverse types of cytokines, in majority pro-inflammatory cytokines like IL-1α, IL-6, TNF-α. While ACAAs could also target some other cytokines i.e. IL-2, CCL3 (T1D) [23,24] IL-3 (Felty's syndrome) [25] BAFF, APRIL (CVID or sIgAD) [26] suggesting the phenotype of these cytokines may not be directly associated to ACAAs secretion. Most of the autoimmune diseases involving ACAA are systemic likely to RA [15-17] SLE [27] MS [22] SS [20,21] and Type 1 diabetes (T1D) [23,24] and some others likely to pulmonary alveolar proteinosis (PAP) [28] Interstitial lung disease (ILD) [29] are local diseases. Overall, the presence of ACAAs is not considered as direct pathogenic factor of the autoimmune diseases. (Table 1) also summarizes the correlation between the titer of ACAA and clinical significance of these autoimmune diseases. Half of these cases were not associated to the disease severity, while some cases showed significant correlation of elevated titer of these ACAAs and disease severity i.e. RA, MS, Osteoarthritis (OA) [30] APECED [8,31] IPEX [10] and T1D [23,24] Of interest, for the same type of autoimmune disorder, regardless different types of ACAAs were consistently detectable, the correlation between ACAAs and clinical relevance was not always in the same line, like SLE [18,19] To summarize, some cytokines are related to the pathological stage of autoimmunity RA and IL-1α, Psoriasis and IL-17A, SLE and IFN-α-thus secretion of these ACAAs should be protective against the development of the disease. However, for some cases correlation cannot be fully established between the secretion of these cytokines and the production of these ACAAs.

Table 1: Clinical impact of autoantibodies targeting cytokines in autoimmune diseases.

Diseases	Cytokines	Clinical relevances
RA	IL-1α	Higher titer associated with benign form, lower CPR and ESR [16]
Psoriasis	IFN-α	No association between severity and anti-cytokine Abs [70]
	TNF-α	No association between severity and anti-cytokine Abs [71]
	IL-22	No association between severity and anti-cytokine Abs [73]
	Il-17A	High titer of anti-cytokine Abs associated with severity [73]
MS	TNF-α, IFN-a, IL-4, IL-10	High titer of anti-cytokine Abs associated with severity [22]
Osteoarthritis	OPN(ETA-1)	High titer of anti-cytokine Abs associated with severity [74]
SLE	IFN-α	Not clear [75]
	GM-CSF	High titer of anti-cytokine Abs with neutropenia [76]
SSc	IL-6	High titer associated with severity with the limited form. High titer correlates to SSc positive patients. [77]
APS-1/ APECED	IL-17, IFN-a, IL-22	High titer of anti-cytokine Abs associated with APS-I causing CMC [58,59]
	IFN-ω, IFN-α2	High titer in patients [59]
T1D	IL-2	High titer associated with increased incidence of diabetes [78]
	CCL3	Positive for new-onset patients [24]
FS	IL-3, GM-CSF, G-CSF	High titer of anti-cytokine Abs associated with cytopenia, only associated to IL-3 [25]
PAP	GM-CSF	No association between severity and anti-cytokine. Sensitive and specific biomarker [28]
PAD/CVID	BAFF, APRIL, IL-21	No association between severity and anti-cytokine Abs [26]
MG	IFN-α, IFN-ω, IL-12	No association between severity and anti-cytokine Abs [79]
ILD	IL-1α	High titer of anti-cytokine Abs associated with severity [80]
SS	IFN-γ, -α and, -ω	No association between severity and anti-cytokine Abs [20,21]
SCID	IFN-α or -IFN-ω or IL-12	High titer of anti-cytokine Abs associated with severity [81]
IPEX	IFN-α	High titer of anti-cytokine Abs associated with Treg deficiency [10]
Pure red-cell aplasia	EPO	High titer of anti-cytokine Abs associated with low red blood cell from bone marrow [72]

Note: ACAA: autoantibodies against cytokine, RA: Rheumatoid Arthritis; MS: Multiple Sclerosis; SLE: Systemic Lupus Erythematosus; SSc: Systemic sclerosis; .APS-1: Autoimmune polyglandular syndrome type 1; APECED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; T1D diabetes; FS: Felty's syndrome; PAP: Pulmonary Alveolar Proteinosis; CVID: Common variable immunodeficiency; PAD: Peripheral artery disease; MG: myasthenia gravis; ILD: Interstitial Lung Disease; SS: Sjorgen's Syndrome; SCID: Severe combined immunodeficiency; IPEX: Immunodysregulation polyendocrinopathy enteropathy X-linked

Cases of ACAAs and Clinical Significances Related to Infectious Diseases

Similar types of ACAAs could be found in both autoimmune disorders and infectious diseases, and they are highly potent to neutralize these cytokines. Less cases were reported in particular in chronic mucocutaneous candidiasis (CMCC) [32] oropharyngeal candidiasis (OC) [13] Staphylococcal skin infection [6,13] and in HIV-1 [7] of which immunodeficiency is a hallmark [7] mirrored by those life-threating patients contracting SARS-Cov2 with an immunodeficient profile [5,33] The cytokines that these infectious disease-associated ACAAs recognized, are prone to be inflammatory and antimicrobial. Interestingly, these studies almost all pointed out ACAAs titers are positively correlated to the severity and incidence of infection, suggesting the hypothesis of 'cytokine deficiency [1] In particular, some of these infections were of primary immunodeficiency which could result in the onset of autoimmune disorders, but also other infections (case of CMCC and OC or staphylococcal skin infection). Likely, the secretion of these ACAA is not a consequence of the infectious diseases but other mechanisms mediating this immune process. An updated list of infectious disease-associated ACAA was shown in (Table 2).

Table 2: Clinical relevance of infectious diseases with regards to autoantibodies production against cytokine-related infection.

Disease	Cytokines	Clinical relevance
SARS-CoV-2	IFN-α2 and IFN-ω	High titer of anti-cytokine Abs associated with severe pneumonia [5]
Disseminated non-tuberculous mycobacterial disease	IFN-g	High titer of anti-cytokine Abs associated with severe mycobacterial infection [65]
	IFN-g	High titer of anti-cytokine Abs associated with severe mycobacterial infection [4]
chronic mucocutaneous candidiasis (CMCC)	IL-17α, IL-17F, and IL-22	High titer of anti-cytokine Abs associated with CMC associated to APS-I [31,32]
oropharyngeal candidiasis (OC)	IL-22	High titer of anti-cytokine Abs associated with OC associated to APS-I [13]
	IL-17A, IL-17	High titer of anti-cytokine Abs associated with OC associated AIRE deficiency [13]
Staphylococcal skin infection	IL-17A, IL-17F, and IL-22	High titer of anti-cytokine Abs associated with CMC associated increased incidence of skin infection [66,67]
	IL-6	High titer of anti-cytokine Abs associated with CMC associated increased incidence of skin infection [6]
HIV	TNF-α	High titer of anti-cytokine Abs associated with infection severity [7]
Invasive, non-typhoidal Salmonella infection	IFN- g	High titer of anti-cytokine Abs associated with infection severity [68,69]
Cerebral Cryptococcus gattii infection	GM-CSF	High titer of anti-cytokine Abs associated with infection severity [41,62]
Invasive staphylococcal infections	IL-6	High titer of anti-cytokine Abs associated with infection severity [6]
Pneumococcal infections	IL-6	High titer of anti-cytokine Abs associated with infection severity [55]

Note: ACAA: autoantibodies against cytokine, HIV: human immunodeficiency virus, Abs: antibodies

Involvement of Primary Immunodeficiency

It is recently considered that, the presence of ACAA is linked to PIDs [34] resulting in disorders of humoral immunity [35] (B-cell differentiation or antibody production), cellular immunity (T-cell defective functions) or even combinatorial B-cell and T-cell abnormalities, as a result of genetic defects [1,9,11] Regardless, PIDs are of a generic description of immune response dysfunction comprising 400 different types, and different pathological manifestations of PIDs could be partly shared. The majorly described types of PIDS involve Autoimmune Lymphoproliferative Syndrome (ALPS) [36,37] APS-1/APECED [38] B-cell expansion with NF-κB and T-cell anergy (BENTA Disease) [39] Caspase Eight Deficiency State (CEDS) [40] Immunodysregulation polyendocrinopathy enteropathy X-linked (or IPEX) [10] all of which were characterized by a particular genetic disorder and showed significant increase of ACAA titers against cytokines shown in (Table 3). As mentioned above, the reported cases of ACAAs were not overall present for all these PID patients, which were previously described, and so far, the presence of ACAA was only documented in APS-1/APECED patients contributing to autoimmune disorders, the other reported cases were of infectious disease including majorly bacterial pathogens. These infections were partially associated to different levels of primary

immunodeficiency described in (Table 3). Interestingly, for those primary immunodeficiencies, several genes affected by the primary immunodeficiency contributing to the function of these cytokines could differentially affect the production of ACAAs. So far, PID leads to majorly opportunistic infection, i.e. Pulmonary alveolar proteinosis and Staphylococcal skin infections in which defect of several genes was involved, which could be mirrored by the effect of deficiency of cytokines regulating anti-pathogen immune response [41] Nevertheless, the observation could not well explain how primary immunodeficiency affects autoimmune disorders despite of APS-1/APECED patients with AIRE gene deficiency [8] which indicates other molecular mechanisms are probably involved in the progression of these diseases.

Table 3: Influence of gene mutation on the secretion of ACAAs.

Primary immunodeficiency	Gene affected	Cytokines	Correlation between PID and ACAAs
APS-1, APECED	AIRE	IL-17, IFN- α, IL-22	Correlated [58]
	IFN	IFN- ω, IFN-α2	Correlated [59]
	RAG1, NFKb2	IFN-α	Correlated [10]
Environmental mycobacterial infection	IFNG	IFN- γ	Correlated [60]
Invasive, non-tyroidal Salmonella infection	IFNGR1, IFNGR2	IFN- γ	Correlated [61]
Pulmonary alveolar proteinosis	CSF2RA, CSF2RB	GM-CSF	Not Correlated [24, 62]
Staphylococcal skin infections	IL-6R, MyD88, IRAK4	IL-6	Not Correlated [6,63,64]
IPEX	FOXP3	IFN-α	Correlated [10]

Note: ACAA: autoantibodies against cytokine, APS-1: Autoimmune polyglandular syndrome type 1, APECED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, IPEX: Immunodysregulation polyendocrinopathy enteropathy X-linked

Defective T Cells Tolerance Hypothesis

So far, APS-1/APECED patients with AIRE gene deficiency were shown to induce autoantibodies secretion against cytokines in homeostasis status, but also against other auto-antigens, which triggered different types of subsequent autoimmune disorders including hepatitis, severe malabsorption, and tubule, interstitial nephritis, Type I diabetes (T1D). The clinical consequences of Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, one remarkable case involving ACAA secretion, are mediated by genetic mutation introduced in the chromosal level, leading to transcription factor Foxp3 erroneous expression (located in chromosome Xq11.23-Xq13) [10] This abnormality eventually results in the loss or dysfunction of immunosuppressive Treg cells [42,43] T. Therefore T cell tolerance breakdown in the periphery, essentially results in the augmented secretion of ACAAs against IFN-α, actively involved in the pathogenesis of different autoimmune diseases where ACAAs could be detected (Table 1). Differently, APECED patients may manifest a superior degree of immune disorder by loss of expression of tissue-restricted antigens (TRA) in the thymus which leads to selection dysfunction of central tolerance impacting all the T cell populations and subsequently B cell function [44,45].

Defective B Cell Tolerance Hypothesis

To another fundamental immunology point of view, plasma cells are terminally differentiated and non-dividing effectors of B cells producing and secreting antibodies, through long-lasting positive and negative signals via B-cell receptor (BCR) along with competition for survival factors such as BAFF (B cell activation factor). Overexpression of BAFF leads to increased number of B cell repertoire that have passed through selection process, including a lot of autoreactive B cells which escaped from bone marrow and periphery, and underwent deregulated BCR signaling they receive [46,47]. The process consisting of selection defect, but also unregulated secretion of BAFF, altogether leads to overexpression of antibodies which could involve ACA [26]. The B cell development related to ACAAs production is supposed to pass through canonical pathways of activation like other antibodies following successful maturation of immunoglobulin on the B cell surface, which suggests BCR signaling was not affected in the anti-cytokine antibodies producing cells. Elevated ACAAs in the sera of PAD/CVID patients were found against BAFF, APRIL (another B cell maturation cytokine), and IL-21 [48] but they were not associated with clinical outcomes, as this was contradictory to the function of BAFF and APRIL and the mature phenotype of T cells [26]. However, another study on PAD/CVID showed defective B cell tolerance on B cell receptor editing [9,49] in turn results in autoreactive B cell clone overproduction. To present B cell antigens, B cells form immunological synapses upon engagement of their B cell receptor (BCR) that is exposed at the surface of antigen presenting cells (APC). Synapse formation between B cells and APC promotes the extraction and the processing of immobilized antigens for presentation on MHC class II molecules to primed CD4+ T cells [48,50] Different from T cell tolerance, B cell tolerance occurs in the bone marrow and periphery, where thymic defect may not be directly mirrored by autoreactive B cell development but through T cells [51].

In the same page, primary immunodeficiency indeed was also shown associated to B cell-tolerance breakdown [52] reflected by the observation in MS patients with IPEX syndrome, manifesting

impaired Treg production therefore accumulated autoreactive B cell clones [53]. The antibodies produced by these clones target not only cytokines but other self-antigens involved in MS patients [53]. Many different clinical cases have been also found with B-cell development associated genetic defects, regardless in the central or in the periphery, both of which direct the decrease of immature and mature antibody secreting cells leading to infection due to the loss of protection by B cells, which is in contradiction to ACAAs development [9].

ACAAs, Biomarkers of Autoimmune Diseases and Infectious Diseases?

Persistent detection of ACAAs in autoimmune diseases and infectious diseases draws attention to use them as biomarker for prognosis and diagnosis, but also for therapeutic targets. Herein, for autoimmune diseases, several different cases have been repeatedly documented, which demonstrates the association of disease severity and the increase of certain ACAAs [22,25,54-59]. However, some contradictory results have also been observed in the same type of pathology, suggesting a more comprehensive analysis is required:

1) The disease progression of patients
2) The phenotype of different ACAAs and
3) The consequences of these ACAAs involved in the diseases.

For infectious diseases, the link between the ACAAs and disease progression is clearer, reflected by the correlation between the infection severity and ACAAs secretion [4,7,13,31,32,41,60-64]. In particular the cytokines recognized by these ACAAs are pro-inflammatory leading to 'cytokine deficiency', which has negative clinical outcomes for the patients. For certain diseases, i.e. SARS-CoV-2, HIV and other bacterial infections, ACAAs against these cytokines could be relevant to stratify the stages of the diseases. At the end, these molecules are considered important evidences of primary immunodeficiency, which could be explained by the defect of genes involved in the production of these cytokines (Table 3).

Discussion

Autoantibodies to cytokines could lead to severe clinical consequences, as observed in several autoimmune diseases, i.e. RA, MS, SSc, T1D, APS-1, infectious diseases i.e. microbial infections, and in particular those ''idiopathic'' diseases (Tables 1 & 2). Clinical relevance of a certain number of autoimmune diseases is associated with elevated titers of different cytokines, including majorly proinflammatory cytokines, IFN and TNF families. It could also affect some other cytokines involved in the adaptive immune responses i.e. on B cell [65,60], T cell but also other hematopoietic cells. The titers of these ACAAs are not always comparably similar in both healthy donors and patients. Moreover, some cases of healthy donors have been shown to have similar titers of ACAAs compared to patients [10,20,25,66] suggesting ACAAs production may not be consistent markers for all the diseases, and a more stratified categorization of the disease progression is needed to perform these correlation studies. Regarding ACAA-mediated infectious diseases, cytokine deficiency is the key to explain why these rare and atypical infections occur related to increase of ACAAs in the serum. These cytokines, utilized majorly by effector T cells engaged in pathogen clearance are in a comparably low level which leads to an impaired T cell function. Of note, several cases are associated to PIDs, suggesting ACAAs are of consequences of PID-associated genetic defect, which could be explained by the mechanisms contributing to cytokine deficiency. However there are few evidences showing the direct link between these types of genetic defects and ACAAs. Furthermore, we challenged the hypothesis of B-cell and T-cell tolerance breakdown leading to these ACAA production. Several cases of ACAAs are somehow directly associated to T-cell tolerance in the level of T cell function, which may subsequently impact autoreactive B cell proliferation. Of note, cases of primary B-cell immunodeficiency (B-PID), one type of B-cell tolerance defect, have been reported with the increases of different cytokines with genetic defect of protein kinase C (PKC) δ showed overexpressed IL-6 and IL-10 in the serum [49].

It would be interesting to see if the link between overproduction of cytokines and ACAAs could be established in this study. Altogether, B-cell tolerance mechanism may not be directly linked to ACAAs [67,68] but in a larger spectrum of autoantigens including the cytokines which could be triggered by other PID mediating different autoimmune diseases or infections. Identification of ACAAs is indeed very critical, and could improve our understanding about the prognosis at early stage, and the treatment of these diseases. For the prognosis, more sensitive multiplex ELISA specific for different types of ACAAs should be developed to follow from early stage the progression of disease. Some other approach using serum filtrating system by removing ACAAs may be of interest [29]. Eventually, a deeper genetic defect identification method based on multi-omics and deep learning should be developed to help to predict the correlation between ACAAs and progression of a certain kind of autoimmune disease or infection. At the end, the studies on the correlation of ACAAs, immunodeficiency and tolerances are to be intensively performed to use them as prognosis markers. Altogether, understanding the role of these ACAAs could help develop better targeted therapies, including monoclonal antibodies against the cytokines involved in the pathogenesis of diseases or antagonist against ACAA production when they are associated to the disease progression [69-80].

Conclusion

In this review, we described the appearance of ACAAs, and their correlations with different clinical consequences. First of all, we summarized all the studies in autoimmune diseases where the role of ACAAs is not fully associated to disease progression, and different types of cytokines are shown to contribute differentially to autoimmune diseases. While ACAAs have a preferential contribution to increase susceptibility to infections by a large spectrum of microbe pathogens. Primary immunodeficiency may be one mechanism that contribute to the secretion of ACAAs while its outcome may not be consistently associated, suggesting a multiple layer of immune defect may be engaged, leading to T cell and B cell tolerance in particular,

which are proposed to be direct consequences of ACAAs productions. However, the link between the pathogenesis of these diseases and the ACAAs production, is not fully supported by the studies from which a lot of researches are to be done. To the end, we recapitulated how we could benefit from the identification of ACAAs and their associated clinical outcomes, to develop better prognosis markers and more efficient therapies against autoimmune diseases, primary immunodeficiency but also infections associated to these immune disorders.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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