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Review

Emerging clinical phenotypes associated with anti-cytokine autoantibodies

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ABSTRACT

Anti-cytokine autoantibodies (AAbs) are frequent and involve a very large panel of cytokines both in healthy subjects and in patients with various pathological conditions. In healthy individuals, anti-cytokine AAbs are described as a part of the natural AAb repertoire and are thought to contribute to the fine regulation of cytokine homeostasis. In some patients, neutralizing AAbs targeting cytokines required for the immune protection against specific microbes may induce acquired immunodeficiency leading to very specific infectious phenotypes. For instance, anti-IFNγ AAbs may induce disseminated non-tuberculous mycobacterial infections; anti-IL-17 AAbs are associated with the development of chronic mucosal candidiasis, and anti-IL-6 AAbs with severe staphylococcal or streptococcal infections. In patients with autoimmune diseases, AAbs directed against pathogenic cytokines are able to influence the course of the diseases. In lupus patients, neutralizing anti-IFNα and anti-TNFα AAbs are associated with a decreased bioactivity of the corresponding cytokine and a lower disease severity. Similarly, anti-IL-1α AAbs are associated with nondestructive forms of chronic polyarthritis. More surprisingly, neutralizing anti-BAFF AAbs are observed in the serum of lupus patients with elevated IFNα signature and higher disease activity. In this review, we summarize the current literature describing the different phenotypes and the main mechanisms associated with the occurrence of anti-cytokine AAbs.

Contents

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1. Introduction

Screening strategy used for the identification of autoantibodies (AAbs) is usually based on indirect immunofluorescence assay using tissue sections or cultured cell substrates. However, notwithstanding numerous advantages, this strategy fails to identify a large amount of AAbs, especially those directed towards soluble antigens, such as anti-cytokine antibodies. The cytokine superfamily includes proteins such as interleukins, lymphokines, interferons, and chemokines, which are important components of the immune system. They contribute to the fine regulation of the protective physiological immune response but they also play crucial roles in pathogenic inflammatory states observed in numerous diseases. Recently, studies using high-throughput protein microarrays and particle-based multiplex assays highlighted that anti-cytokine AAbs are frequent and involve a very large panel of cytokines, chemokines and growth factors [1,2]. They are observed both in healthy individuals and associated with various pathological conditions. Neutralizing AAbs targeting cytokines required for the immune protection against specific microbes (e.g. IFNγ, IL-6, IL-17, GM-CSF) may induce acquired immunodeficiency leading to life-threatening infectious complications (Table 1). On the other hand, AAbs targeting cytokines involved in the pathogenesis of inflammatory diseases (e.g. TNFα, IFNα, BAFF, IL-1α) are able to influence the course of these diseases and may become interesting biomarkers in disease monitoring (Table 2). However, most of the time, anti-cytokine AAbs are observed in healthy subjects and seem to belong to the natural AAb repertoire with important functions in the regulation of cytokine homeostasis. In this review, we present the mechanisms and the different phenotypes associated with the occurrence of anti-cytokine AAbs and discuss their clinical relevance in infectious, inflammatory and autoimmune diseases.

2. Anti-cytokine autoantibodies associated with acquired immunodeficiencies and opportunistic infections

2.1. Anti-IFNγ autoantibodies

IFNγ and TNFα are two major effector cytokines involved in the adaptive cell-mediated immune response (Th1 pathway), dedicated to host defense against viruses and other intracellular pathogens. Genetic inherited disorders of the IFNγ pathway lead to severe opportunistic infections occurring generally in early childhood, often showing familial clustering and frequently involving mycobacteria, salmonella and some viruses [3–5]. The occurrence of such infections in adults without any obvious genetic or iatrogenic origin points out two main potential etiologies: human immunodeficiency virus (HIV) infection and neutralizing anti-IFNγ AAbs. Several cases of opportunistic infections related to the occurrence of neutralizing anti-IFNγ AAbs were described since 2004 [6–17]. The patients, originated from South-East Asia for most of them, develop rapidly growing disseminated nontuberculous mycobacterial infection with or without concomitant or delayed other opportunistic infections usually observed in HIV patients such as non-Typhi salmonellosis, Histoplasmosis, Cryptococcosis, varicella-zoster virus infection, or penicilliosis [6–17]. In a recent study involving 203 HIV-negative patients from Taiwan and Thailand presenting with adult-onset disseminated mycobacterial infection with or without other opportunistic infections, high concentration of neutralizing anti-IFNγ AAbs was detected in more than 80% of patients [6]. The occurrence of anti-IFNγ AAbs strongly correlated with an increased risk of developing disseminated nontuberculous mycobacterial infection and only slightly increased the susceptibility to *Mycobacterium tuberculosis*, suggesting distinctive roles for IFNγ in the control of the different mycobacterial species. In three individuals with high anti-IFNγ AAb titers but without opportunistic infections, the AAbs were devoid of any IFNγ-blocking activity. More surprisingly, neutralizing anti-IFNγ AAbs were the unique biological factor found to distinguish patients with or without adult-onset disseminated opportunistic infections. Indeed, among 40 other anti-cytokine AAbs assayed, only one patient with cryptococcal meningitis and pulmonary tuberculosis had AAbs against granulocyte-macrophage colony-stimulating factor (GM-CSF). No other anti-cytokine AAbs or genetic defects were found to be associated with opportunistic infections [6]. Although the pathogenic process leading to the tolerance breakdown to IFNγ remains unknown, the fact that nearly all of the patients identified to date with this phenotype were Asia-born Asians strongly suggest the involvement of both environmental and genetic factors. A recent study showed that the presence of neutralizing anti-IFNγ AAbs in adults with disseminated nontuberculous mycobacterial infections is strongly associated with HLA-DRB1*16:02 and HLA-DQB1*05:02 alleles [18]. Nevertheless, very few cases were described in Asians born outside of Asia suggesting the additional contribution of environmental factors.

2.2. Anti-IL-17 autoantibodies

Autoimmune polyendocrine syndrome type 1 (APS-1), also known as autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED), is a rare autosomal recessive genetic syndrome

Table 1
anti-cytokine AAbs associated with acquired immunodeficiencies.

Cytokine target of AAbs	Clinical presentation	Associated infections	References
IFNγ	Opportunistic infections in patients originated from South-East Asia	Rapidly growing disseminated nontuberculous mycobacteria, *Mycobacterium tuberculosis*, *Salmonella*, *Histoplasma*, *Cryptococcus*, *Penicillium*, varicella-zoster virus	[6–14,18]
IL-17	APS-1/APECED	Chronic mucosal candidiasis (CMC)	[22–24,27]
IL-6	Severe and recurrent bacterial infections with paradoxical low levels of serum CRP	*Staphylococcus aureus*, *Escherichia coli* and *Streptococcus intermedius*	[29,30]
GM-CSF	PAP and/or opportunistic infections	Nontuberculous mycobacteria, *Histoplasma*, *Cryptococcus*, *Nocardia* or fungi	[33–40]

APS-1: Autoimmune polyendocrine syndrome type-1; APECED: Autoimmune PolyEndocrinopathy with Candidiasis and Ectodermal Dystrophy; PAP: Acquired pulmonary alveolar proteinosis.

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