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Survey

High avidity cytokine autoantibodies in health and disease: Pathogenesis and mechanisms

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ABSTRACT

Numerous reports have documented the presence of autoantibodies working against naturally occurring cytokines in humans in health and disease. In most instances, their physiological and pathophysiological significance remains unknown. However, recent advances in the methodologies for detecting cytokine autoantibodies and their application in research focused on specific disorders have shown that some cytokine autoantibodies play an important role in the pathogenesis of disease. Additionally, levels of cytokine autoantibodies may also correlate with disease severity and progression in certain infectious and autoimmune diseases but not in others. This suggests that cytokine-specific pathogenic differences exist. While multiple lines of evidence support the notion that high avidity cytokine autoantibodies are present and likely to be ubiquitous in healthy individuals, their potential physiological role, if any, is less clear. It is believed that they may function by scavenging pro-inflammatory cytokines and thereby inhibiting deleterious 'endocrine' effects, or by serving as carrier proteins, providing a 'reservoir' of inactive cytokines and thus modulating cytokine bioactivity. A central hypothesis is that sustained or repeated high-level exposure to cytokines triggers defects in T-cell tolerance, resulting in the expansion of existing cytokine autoantibody-producing B cells.

Contents

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1. Introduction

In 1981, antibodies against interferon (IFN)-α or IFN-β were reported in participants of clinical trials evaluating administration of these exogenous recombinant human cytokines [1,2]. Less than a decade later, naturally occurring autoantibodies against endogenous interleukin-1α (IL-1α) were reported [3,4]. Cytokine autoantibodies have been identified in pharmaceutical preparations of intravenous immunoglobulin (IVIG) and in the healthy subjects from whom IVIG were derived [5–9]. Numerous studies have additionally demonstrated that cytokine autoantibodies are detectable in health and disease in various tissues, including blood [3,4,7,10–14], lung [10,15–17], pleural fluid [18], central nervous system [19], gums [20] and synovial fluid [21,22]. In some cases, specific autoantibodies have been implicated in disease pathogenesis or predisposition [10,14,16–18,23–27]. Others appear to be responsible for the associated physical manifestations of disease [28–30]. In addition to blocking specific cytokine function, cytokine autoantibodies may play an important role in health and disease by virtue of their ability to form immune complexes [12,13,16,17,31–33], which can interfere with their detection by conventional cytokine 'antigen-capture' methods [12,13]. The recent development of novel methods has improved our ability to detect cytokine autoantibodies and has enhanced our understanding of their role and function. In this report, we review the current literature relating to the presence, biological function, potential mechanisms of production and significance of cytokine autoantibodies.

2. Cytokine autoantibodies in disease

Cytokine autoantibodies have been detected in patients with various diseases (Table 1). In order to explore the pathogenic roles of cytokine autoantibodies in each of these diseases, we discuss (1) the role of each cytokine in the given disease, (2) the incidence of autoantibody detection in the disease, (3) the mechanism of their function in disease pathogenesis, and (4) reports detailing the association of autoantibodies with certain therapies or clinical manifestations. In each case, the effects on disease pathogenesis or severity were linked to the biologic function(s) regulated by the specific cytokine and the interrelationship of this regulation with other members of the cytokine regulatory network (Fig. 1).

Table 1
Cytokine autoantibodies found in individuals diagnosed with a clinical disorder.

Cytokine	Tissue	Diseases	Neutralizing	Comments	References
IL-1α	Blood	RA, SjS, MCTD, PM, SLE, self-limiting synovitis	Yes	Autoantibody levels are inversely correlated with disease severity in	[3,9,28,29]
IL-1β	Blood	RA	Yes	patients with arthritis.	[3]
IL-2	Blood	HIV		Anti-gp41 antibody cross-reacts	[54,67]
IL-4	CNS, Blood	MS, AM, stroke, lung infection		with human IL-2.	[19,92]
IL-6	Blood	SSc, RA, PM, DM, SLE, MCTD, alcoholic LC, recurrent bacterial infection	Yes	Potential carrier protein in SSc. Positive autoantibody in LC is related to a high frequency of infection and high mortality *in vivo*. IL-6-autoantibody may impair the immune response in infection.	[9,26,32,45,48,93]
IL-8	Lung, Blood, Gum, SF	ARDS, ovarian cancer, periodonitis, arthritis		Presence of IL-8-autoutoantibody complexes is a prognostic indicator of ARDS. Kd = 4.6–8.5 pM. Potential transmitter via FcR.	[15,16,20,22,31,46,47,94]
IL-10	Blood, CNS	MS, AM, Stroke			[19]
IL-12	Blood	thymoma ± MG, RA, SLE, infection	Yes	Viral infection including HIV and hepatitis virus.	[50,57,95]
TNF-α	Blood, CNS	SLE, HIV, GNB, RA, MS, AM		Decreased autoantibody level is related to active SLE *in vivo*.	[19,30,52,96,97]
G-CSF	Blood	FS, SLE	Yes	Associated with neutropenia.	[23]
GM-CSF	Blood, lung	Autoimmune PAP, thymoma ± MG, PM, DM	Yes	Inhibits Mϕ and neutrophil function by blocking GM-CSF signaling. Kav = 20 pM.	[10–12,14,17,34,50,98,99]
IFN-α	Blood	Infection, APS-1, SLE, MCTD, PM, RA, thymoma ± MG, SCLS, paraneoplastic syndrome	Yes	Autoantibodies are believed to be critical in the pathogenesis of autoimmune PAP.	[9,27,49–51,53,57,100]
IFN-β	Blood	Thymoma ± MG, SLE, RA, SCLC	Yes		[50,100]
IFN-ϖ	Blood	APS-1, thymoma ± MG, RA, SLE	Yes		[27,50,100]
IFN-γ	Blood, CNS, PF	MS, AM, SLE, infection,	Yes	Potentially related to lowly virulent bacterial	[18,19,25,39–41,95,100,101]
EPO	Blood	PRCA, SLE	Yes	infection (e.g., M. tuberculosis, NTM).	[24,37,38]
NGF	Blood, SF	SLE, autoimmune thyroiditis, RA, spondylarthropathy, mental disorder		Potential carrier protein.	[21,102]

Abbreviations: AM, aseptic meningitis; APS-1, autoimmune polyendocrine syndrome-1; ARDS, acute respiratory distress syndrome; CNS, central nervous system; DM, dermatomyositis; FcR, Fc receptor; FS, Felty's syndrome; GNB, gram negative bacteria; HIV, human immunodeficiency virus; Kav, avidity; Kd, dissociation constant; LC, liver cirrhosis; Mϕ, macrophage; MCTD, mixed connective tissue disease; MG, myasthenia gravis; MS, multiple sclerosis; NTM, nontuberculous mycobacteria; PAP, pulmonary alveolar proteinosis; PF, pleural fluid; PM, polymyositis; PRCA, pure red-cell aplasia; RA, rheumatoid arthritis; SCLC, small cell lung cancer; SF, synovial fluid; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc: systemic sclerosis.