Reviews

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INTERLEUKINS AND THEIR AUTOANTIBODIES IN HEALTH AND DISEASE

Anti-interleukin autoantibodies (AIAs) are a unique type of immunoglobulins that target the human own ILs, which are key protein mediators of the immune system. Although the presence of AIAs is mostly associated with several immunodeficiency conditions, recent studies show that their presence in healthy individuals is normal, however in small amounts. In addition, the elevated titters may also be a marker of a positive prognosis or even a decrease in the severity of some diseases. Research into AIAs opens up new perspectives for understanding the pathogenesis of autoimmune and infectious diseases, as well as for the development of new approaches to effective and targeted therapy.

Keywords: *interleukins, anti-cytokine autoantibodies, anti-interleukin autoantibodies, rheumatoid arthritis, acute respiratory distress syndrome, asthma, autoimmune polyendocrine syndrome type 1.*

Introduction

Cytokines (CKs) are specialized small soluble proteins that have a unique set of functions, and play a crucial role in the immune system interactions, while their dysfunction can lead to some severe pathologies. This indicates their important role during chronic (ChD), autoimmune (AD), and infectious (ID) diseases. Therefore, the ability to accurately evaluate CKs using laboratory methods is of particular importance, which is limited by several factors, including some natural obstacles [1, 2]. CKs can be classified into several categories: interferons (IFNs), growth factors, tumor necrosis factors, interleukins (ILs), and chemokines (ChKs), which can act functionally as modulators of cell activity (regulators) or as direct inducers of immune processes (effectors) [1, 3].

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ILs are pleiotropic CKs that finely regulate cellular interactions within the innate and adaptive immune systems. They modulate signaling cascades that determine the polarization of the immune response, the balance between pro- and anti-inflammatory reactions, and maintain the homeostasis of hematopoietic populations. Their investigation is fundamental to elucidate the molecular mechanisms underlying immunopathologies and to develope targeted biotherapeutic strategies.

It has been established that autoreactive B-cells in response to the interleukin autoantigens can produce antibodies against them, which can have various effects on ILs functionality, leading to the exceptional and complex changes in the course of various diseases [103], although the causal relationships in processes associated with AIAs remain a controversial issue.

The aim of this study was to summarize the current literature on the group of interleukins, which we consider to be the most significant, to examine the mechanisms underlying the development of autoantibodies against them in both patients and healthy individuals, and to outline future research directions regarding their role in chronic, autoimmune, and infectious diseases.

A short overview of specific ILs

ILs are one of the superfamilies of CKs produced by various types of cells and perform a complex of functions to ensure the functioning of the immune system. They play an important role in maintaining immune homeostasis and protecting the body from pathogenic microorganisms (MO). They are traditionally subdivided into pro- and anti-inflammatory, although the relationship of ILs to one group or another is conditional, since their different and even opposite effects on the body can be caused by various factors (such as concentration in biological fluids, target cell type, duration of exposure *etc.*) [4, 5].

Based on the literature, ILs can be classified into seven families [6—13], several individual members (IL-14, IL-32, IL-34) [6, 8], which also may include some recently described IL-40 and IL-41 [14, 15], while IL-8 (CXCL-8) and IL-16 are more closely associated with ChKs [6, 16].

In the context of further study of AIAs, in this section we provide the summary of general characteristics of key interleukins (Tabl. 1).

IL-1 family: IL-1 and IL-33. **IL-1.** Pro-IL-1α is constitutively present in most human cells and is biologically active (Tabl. 1), however, in intact cells, its biological activity is restrained by binding to the inhibitory cytosolic receptor IL-1R2, though can be released after cell damage [19], whereas pro-IL-1β has low biological activity: its activation requires processing by NLRP3-inflammasome and caspase-1 [18—20]. Despite the low homology of the gene sequences (less than 26%) encoding IL-1α and IL-1β [19], both forms mediate their functions through IL-1R1 and therefore have similar functions, initiating signaling pathways responsible for the course of the inflammatory process, engaging immune cells, other CKs and inflammatory mediators [18, 19]. IL-1α plays a central role in the pathogenesis of numerous inflammatory diseases (skin, airway and lungs, blood vessels and heart diseases) [19], while IL-1β is absent in cells during homeostasis, but involved in pathogenesis of many autoimmune diseases (e.g., RA and SLE) [18]. IL-1α/β play a predominantly protective role in some fungal and bacterial IDs [20, 21].

IL-33. Pro-IL-33 is already an active form of IL-33 (Tabl. 1); several different proteases cleave it to mat-IL-33, significantly increasing its activity [23, 24], although some caspases can regulate IL-33 activity [23], in particular caspase-1 can convert pro-IL-33 to an inactive form [24].

Pleiotropic IL-33 is involved in a wide spectrum of biological events [22], can act as both a transcription regulator and an extracellular signaling molecule, and affects various innate cells (Mφ, Eos, MCs, and Bas) as well as adaptive immune cells (DC, Th2-, Treg-cells; can activate CD8+-cells) [23, 24]. Elevated levels of IL-33 and ST2 are known to be present in patients with various AD (RA, SLE, IBD, and psoriasis) [24] and ChD (allergic asthma, COPD) [23]. IL-33 also plays an important role in

initiating the immune response to the invasion of various infectious agents by modulating the Th2-response [24—26], in particular, by ameliorating the course of *M. tuberculosis* infection [25]. Depending on the infectious pathogen, its effect can be either protective or harmful [20, 26].

IL-2 family: IL-2 and IL-4. **IL-2**. Promotes activation of the described signaling pathways (Tabl. 1), which are responsible for activity of effector and regulatory T-cells, in particular, IL-2 regulates differentiation of Th-17 cells by modulating IL-6-mediated signaling [29, 30]. In addition, IL-2 plays a crucial role in the establishment of immune tolerance, which, in conjunction with the aforementioned, is particularly significant in the context of antibody generation and the regulation of this process [28].

IL-4, which signals exclusively through STAT6 (Tabl. 1), regulates the differentiation and function of T- and B-cells; affects the ability of B-cells to produce certain types of antibodies (ABs), namely, causes «switching», that stimulate B-cells to produce immunoglobulins of type E (Ig E) instead of type G (Ig G) [6, 31]. IL-13, often considered with IL-4, has a similar structure and can compete with it for some Rs, but does not use the γ-subunit — although it also triggers STAT6 [6, 32]. IL-4 can regulate Th1- and Th17-inflammation, although it can also trigger a potentially harmful Th2-response [32]. It may exacerbate asthma, so it is regarded as a potential therapeutic target; however, for some other diseases (fibrosis, COPD, IBD), the effectiveness of this strategy is less convincing [32, 33].

Table 1. **General characteristics of some IL-superfamily members [14—46]**

CK-family	IL	HG	Cell sources	Structure, size, and forms	Rs	Activation of signal proteins
IL-1	IL-1α	*IL1A*	KCs, Acs, EpCs, EnCs MyCs (d/i)	Already active pro-IL-1α and mat-IL-1α (HtD, 17 kDa)	IL-1R1 + IL-1R3	TAK1, NF-kB, MAPKs (p38, ERKs), AP-1, JNK, and IFN-regulating genes
	IL-1β	*IL1B*	Only d/i, MyCs	Non-active pro-IL-1β; active mat-IL-1β (HtD, 17 kDa)	IL-1R2 + IL-1R3	IL-R2 has a lack of TIR-domain: acts as DR
	IL-33	*IL33*	DCs, FBs, EnCs, EpCs, ACs	Less active pro-IL-33 (30 kDa); More active mat-IL-33 (Mm, 18 kDa)	mST2+IL-1R3;	MyD88– IRAK-TRAF6 axis, NF-kB, MAPKs (p38, JNK, ERK1/2), PI3K-AKT;
					sST2+IL-1R3	DR
					IL-1R8+IL-1R3	IL-1R-signal inhibitor
IL-2	IL-2	*IL2*	T-cells, after antigen stimulation	Mm, 15.5 kDa	IL-2Rα (low affinity)	It triggers downstream signaling only as a part of the complete trimeric receptor complex (IL-2Rα, IL-2Rβ, and γc), but not independently, sIL-2Rα may also act as DR;
					dimeric IL-2Rβ+IL-2Rγ (middle affinity)	JAK-STAT, ERK, PI3K
					trimeric IL-2Rα+β+γ (high affinity)	
	IL-4	*IL4*	CD4+-cells, Bas, Eos, MoCs	Mm, 15 кDa	IL-4R1+IL-4R2	JAK (JAK1, JAK2, JAK3, TYK2)–STAT6

End of the Table 1

CK-family	IL	HG	Cell sources	Structure, size, and forms	Rs	Activation of signal proteins
IL-6	IL-6	*IL6*	LyCs, MyCs, SMCs, bone cells *etc.*	Pro-IL-6 (21—28 kDa) become active (HmD, 19—26 kDa) after its signal segment cleaved	mIL-6Rα+gp130 (classic signaling); sIL-6Rα+gp130 (pathological signaling)	Activation of JAK (JAK1, JAK2, TYK2), which initiates three main signaling pathways: JAK-STAT (STAT1, STAT3, STAT5); JAK-RaF-Ras-MAPK; JAK-PI3K-AKT, which promotes NF-kB activation
ChKs	IL-8 (CXCL-8)	*IL8* (*CXCL8*)	Only d/i: MoCs, FBs, EnCs, EpCs, T- and B-cells, Nφ, SMCs *etc.*	Pro-IL-8 become mat-IL-8 after its signal segment cleaved; there are different forms of mat-IL-8 (based on amino acid sequence; HmD, ~16 kDa)	CXCR1 + CXCR2 (but may perform some HmD-forms); ACKR1	Ras-PI3Kγ-AKT, PL (Cβ2/β3, A2, D) Does not trigger downstream signaling pathways
IL-10	IL-10	*IL10*	LyCs, MyCs, DCs	HmD, 36 kDa	Tetrameric (IL-10RA+ IL-10RB)	JAK1/TYK2–STAT; PI3K-AKT, NF-kB inhibitors (NF-kBIA та NF-kBIE)
	IL-22	*IL22*	LyCs (e.g., Th22)	Mm, 23 kDa	IL-22R1+ IL-10R2; IL-22BP	JAK1/TYK2–STAT3 (also STAT1, STAT5), MAPKs DR
IL-12	IL-12	*IL12A*	Mφ, MoCs, Nφ, DCs	HtD (p40+p35), ~ 40+35 kDa	IL-12Rβ1+ IL-12Rβ2	TYK2/JAK2–STAT4 (also STAT1, STAT3, STAT5), p38, PI3K-AKT
	IL-23	*IL23A*	Mφ, DCs	HtD (p40+p19) ~ 40+18,7 kDa	IL-12Rβ1+IL-23R	TYK2/JAK2–STAT3 (also STAT1, STAT4, STAT5), MAPK and PI3K
IL-17	IL-17A	*IL17A*	Tc-, Th-17-, and NKT-cells;	HmD-IL-17A (35 kDa, high PS)	IL-17RA+IL-17RC	ACT1, MAPKs, NF-κB, C/EBP (β and δ), JAK-PI3K, JAK-STAT;
	IL-17F	*IL17F*	may be produced by Nφ;	HtD-IL-17A/F (middle PS) HmD-IL-17F (low PS)		IL-17A also activates: TRAF4–ERK5, TRIF, MyD88, adaptor proteins

Notes. HG — human gene, Rs — receptors, FBs — fibroblasts, EpCs — epithelial cells, EnCs — endothelial cells, ACs — astrocytes, KCs — keratinocytes, Mφ — macrophages, MoCs — monocytes, Nφ — neutrophils, LyCs and MyCs — lymphoid and myeloid cells, DCs — dendritic cells, PS — power signal, d/i — during inflammation, mat-IL — mature form of IL, Mm — monomeric, HtD — heterodimeric, HmD — homodimeric, mIL-R — membrane IL-Rs, sIL-R — soluble IL-R, DR — decoy receptor, ACKR1 — Atypical chemokine Receptor 1.

IL-6 family. **IL-6.** Binds to mIL-6Rα (Tab. 1), modulating physiological functions (e.g., activates acute phase proteins in the liver) [34, 36], whereas when interacting with sIL-6Rα, it circulates throughout the body until it binds to gp130, forming a trimer, which then binds to another trimer and forms a hexameric receptor complex [34, 36], triggering pro-inflammatory reactions, with the localization of inflammation depending on the location of gp130 [36], which is a key in the context of signaling pathway activation; disturbance in their activity can cause various pathological conditions (RA, IBD, diabetes) [36].

IL-10 family: IL-10 and IL-22. **IL-10.** Plays a key role in modulating inflammation, as it can activate NF-kB inhibitors [38] (Tabl. 1), which restrain the activity of Nφ and Mφ, by limiting their ability to synthesize pro-inflammatory cytokines [39], such as IL-6 and IL-8, as well as IL-1α/β and TNF-α [38, 39]. In addition, IL-10 suppresses the development of pulmonary fibrosis (which can be induced by profibrotic CKs such as TGF-β) and modulates the response to infectious pathogens [39, 40].

IL-22. Its main action is directed at non-hematopoietic EpCs and FBs in internal organs (Tabl. 1), particularly in the lungs, intestines, liver, *etc.* Although its role in the tissue regeneration is certainly important, the same function plays a role in the formation of malignant tumors and psoriasis. The elevated levels are also observed in atopic dermatitis and bacterial ID [41], but during IBD it can induce recovery of the mucosa, although this effect may be reduced by interaction with IL-22BP [42].

IL-12 family: IL-12 and IL-22. **IL-12.** The active form (p40 + p35) is characterized predominantly as a pro-inflammatory IL; p40 can be secreted in the absence of p35 in the form of Mm or HmD, acting as an antagonist of IL-12R. IL-12 controls the differentiation of immature T-cells into IFN-γ-producing Th1-cells; indirectly activates the antimicrobial, antiparasitic, and antitumor activity of Mφ and promotes the cytolytic activity of NK-cells [6, 43] (Tabl. 1).

IL-23. The active form (p40 + p19) is produced in response to Toll-like receptor (TLR) activation, which can be further enhanced after CD-40R activation. In addition, IL-23R production is regulated by IL-6 and IL-21. Unlike IL-12, it plays a role in the development of Th17-cells, promoting antimicrobial immunity; disturbances in IL-23 regulation affect barrier function, manifesting in skin (particularly psoriasis), intestinal, and lung pathologies [6, 43, 44].

IL-17 family: IL-17A and IL-17F. **IL-17A** and **IL-17F.** Well-described pro-inflammatory mediators with many common features [13, 45] (Tabl. 1), signal through the mobilization of Act1, activating NF-kB [45]. Besides, they may also induce some regulatory proteins that inhibit excessive activation of this factor; non-canonical activation of TRAF4-ERK5 stimulates keratinocyte proliferation, which may contribute to tumor development; IL-17A promotes the production of some other proinflammatory cytokines (IL-6 and IL-8) [13, 45].

IL-17 plays a key role in antifungal and antibacterial immunity, namely against the *Candida*, *Cryptococcus*, and *Staphylococcus*. Defects in its signaling pathways lead to severe fungal infections. However, IL-17A may contribute to the development of a pathogenic pro-inflammatory autoimmune response in psoriasis [13]. IL-17F, like IL-17A, also mediates inflammatory responses and barrier surface protection; disruption of IL-17F signaling increases susceptibility to CMC [13, 45]. IL-17-mediated signals also may be enhanced by IL-23 [13, 45].

CXC-subfamily of ChKs. **IL-8.** In recent years it is usually classified into the CXC-subfamily of ChKs because it has a variable amino acid between its N-terminal cysteines [3, 16]. IL-8 promotes Nφ recruitment to sites of inflammation, regulates endothelial adhesion (promoting angiogenesis), and mobilizes leukocytes, including IL-13/IL-4-stimulated MoCs, some T-cells, and MCs [16, 46].

Binding to ACKR1 maintains the IL-8 gradient necessary for Nφ recruitment and may also promote inflammation by transporting and presenting IL-8 to leukocytes, promoting their extravasation. IL-8 is considered a therapeutic target for the treatment of various inflammatory diseases in which Nφ

plays a pivotal role, including cancer (IL-8 is an important mediator of angiogenesis in tumor development) [16], AD and ChD (allergic asthma, COPD, psoriasis, RA, SLE, *etc.*), as well as in sepsis [16, 46].

ILs and their signaling cascades play a key role in homeostasis. In particular, disturbances in these pathways can lead to specific pathological disorders, and in recent years, antibodies to cytokines have attracted particular attention, as their appearance is often associated with various complications in diseases [54].

Potential mechanisms of ACAs generation

The formation of ABs is a key mechanism for the detection and elimination of external antigens by the adaptive immune system [47], and its specificity is crucial, although some ABs reveal multispecific activity, which may result from the actual function of proteins, thus, sometimes this reaction is not directed only against foreign antigens [48].

Autoantibodies (AAs) are abnormal ABs that target the body's own tissues or cells. Some AAs, known as natural AAs, are produced by autoreactive B-cells but do not undergo affinity maturation through antigen stimulation, therefore they react to a wide range of antigens, exhibiting cross-, but not self-specific reactivity [47, 49]. On the other hand, the appearance of AAs can be induced by infections and parasites through mechanisms such as molecular mimicry (MO proteins can cause the formation of cross-reactive Abs. Such reactivity promotes a faster response to new, similar pathogens [49]), release of hidden autoantigens, epitope spreading, and immune dysregulation. Risk factors may include genetic predisposition, innate immune disorders, and excessive inflammation [50, 51]. However, the appearance of natural AAs in small quantities has been recorded both in mice that had no contact with MO [47] and in congenitally healthy individuals [49].

It is generally accepted that AAs arise due to dysfunctional central or peripheral tolerance of B- and T-cells. On the other hand, the significant number of autoreactive B-cells in the periphery has prompted some researchers to propose an alternative concept — "adaptive" tolerance, in which self-reactive B-cells respond to polyvalent autoantigens, so the specific IgD AAs recognize the valence of antigens, while primary IgM eliminates these structures and secondary IgM protects them [52]. This is consistent with a new interpretation of the role of rheumatoid factor, which depends exclusively on its affinity for destructive IgG (low-affinity IgG exhibits neutralizing activity, while high-affinity IgG exhibits protective activity, enhancing their effect) [53], and may indicate the presence of autoimmunity in the normal states, not only in pathological conditions [52—53].

Among the natural AAs that contribute to a better course of diseases, only specific anticancer AAs, which were found in patients with better survival in oncological diseases, and some anti-cytokine autoantibodies (ACAs) have been described [47].

In general, ACAs are a special group of natural AAs that act against certain types of CKs. They are often described as "phenocopies of primary immunodeficiency" capable of altering the nature of the immune response [54]. This is characteristic of pathogenic ACAs, which usually reach concentrations that affect the half-life of CKs and can also disrupt their signaling by overstimulating or, conversely, inhibiting it. They can be found in patients with various AD, including some rare ones [47, 55].

In addition to those described for some natural autoantibodies, the possible mechanisms for appearance of ACAs include a response not only to endogenous CKs, but also a reaction to exogenous cytokine therapy. On the other hand, such a strategy, in combination with other immunosuppressive techniques, in particular the suppression of autoreactive lymphocyte activity, or the reduction of ACAs concentrations through plasma exchange, *etc.*, is used to treat diseases mediated by the pathological effects of ACAs [72].

Furthermore, it has been shown that many ACAs are also found in healthy people [56]. A more recent study with a much larger sample has confirmed that about 86% of healthy patients

had AAs to at least one of the CKs studied (Tabl. 2), confirming the view that neutralizing ACAs are also found in healthy people, but under the level capable of disrupting signaling [57]. This is consistent with the latest study confirming the appearance of AAs in healthy individuals, even during a repeat visit, which may reveal their stability in the short term [58].

It seems that the accuracy of ACAs determination in patients' blood also plays a key role here, and although there are methods for identifying them (ELISA, flow cytometry, *etc.*), only some ACAs show clear activity *in vitro*, which complicates the assessment of their clinical significance [59].

However, a recent study has proposed evaluating not the level of AAs, but their inhibitory effect on the action of CKs, which can be used to detect neutralizing ACAs in diseases caused by the pathogens of severe infectious diseases [60], which is important because ACAs can increase susceptibility to ID by promoting the development of opportunistic pathogens [61].

AIAs and their role in diseases

There are still a relatively small number of studies focused on AIAs. Several researchers have focused on AAs to GM-CSF (in PAP and associated ID) [62], as well as anti-IFN AAs [47], with particular attention to anti-IFN-γ, which, according to one review, were found in a wide range of concentrations in different cohorts of patients with ID caused by more than 30 pathogens [63]. In this review, the focus was on the study of some AIAs (Tabl. 3).

Similar to IL-1RA, neutralizing anti-IL-1 AAs are characterized by their ability to regulate IL-1 signaling. Their presence has been described in various skin diseases [64], although at first no significant difference in the occurrence of these AAs in HS (the etiology of which has not been fully established) has been found compared to healthy individuals [67], subsequent studies have demonstrated elevated levels of anti-IL-1α/β in stage III (as classified by Hurley) in affected skin areas [68], which, combined with previous data, may indeed indicate the central role of IL-1 in the induction of inflammatory skin reactions [64].

There is evidence of an association between anti-IL-1α and a non-destructive phenotype of chronic polyarthritis, as well as with different courses of RA [64, 65], and in SLE in small cohorts of patients [66].

Anti-IL-1α was detected in several patients with IMHC, but was not detected in controls or in patients with Hodgkin's lymphoma, and despite the fact that IL-1β levels are usually elevated in patients with IMHC, no anti-IL-1β was detected in any of the patients [55].

Anti-IL-2 AAs bind to IL-2 in experiments on NOD-mice, the number of which increases with the development of type 1 autoimmune diabetes mellitus. They are also found in people with diabetes mellitus, where they are clonal and have high binding affinity to IL-2, contributing to the disruption of immune tolerance. Their possible origin from the germinal center [69] is confirmed by their detection in healthy people in the form of an AA-CK-complex [56]. Their appearance in

Table 2. **Identification of ACAs to certain CKs in healthy individuals**

Ref.	Anti-IL-1	Anti-IL-2	Anti-IL-4	Anti-IL-6	Anti-IL-8	Anti-IL-10
[56]	–	100%	93.3%	6.7%	100%	73.3%
[57]	48,5%	–	–	65%	–	35.5%
[58], FA	52,3%	–	–	59.9%	–	39.6%
[58], RepA	46,1%	–	–	57.5%	–	33%

Notes. The results are outlined as a percentage of the number of patients. The sign "–" means that the presence of this type of ACAs was not investigated. FA — first analysis, RepA — repeated analysis.

HIV-patients was reported, probably caused by cross-reactivity against the virus capsid protein, which is structurally homologous to IL-2 [70].

In the study of patients with SLE, a significant increase in anti-IL-2 levels in the blood was observed, which was associated with the severity of the disease [71]. The presence of IL-2 in serum at stage II HS and elevated levels in affected skin areas at stage III compared to control and stages I-II have also been reported [68].

Anti-IL-4 AA. Data are remarkably limited; found in tiny amounts in the plasma of healthy donors, in the form of a cytokine-AA complex [56]. No data are available on the association with AD or ID [56, 72].

Anti-IL-6 AA. Anti-IL-2 AAs was first described in patients with alcoholic LC, leading to an increased risk of severe infections and mortality [54, 72].

Anti-IL-6 AAs were subsequently detected in a boy with a severe form of skin disease caused by *Staphylococcus aureus*: clinical symptoms included cellulitis and subcutaneous abscesses [73]; also in two patients (a 67-year-old man with empyema caused by *Staphylococcus intermedius* and *E. coli*; and a 56-year-old woman with multiple subcutaneous abscesses, suffering from RA and receiving treatment with sodium aurothiomalate for 30 years) [74]; and in several cases of septic shock: a girl was found to have AAs to IL-6, leading to a more severe *S. aureus* infection [75] and in a 62-year-old woman (caused by *Eggerthella lenta*) who received anti-cancer treatment with durvalumab in combination with platinum-based chemotherapy (may have occurred as a side effect) [76].

In all these studies, low CRP-levels were recorded in the presence of an obvious inflammatory process, which clearly supports the idea that this feature can be used as a marker for the appearance of these AAs in severe disease [73—76]. However, in HS, where *S. aureus* is often detected, the difference in AAs to IL-6 relative to the control is not statistically significant; anti-IL-6 probably does not play a significant role in the pathogenesis of this disease [67].

As mentioned earlier, anti-IL-6 was also found in healthy individuals, but interestingly, the level of anti-IL-6 was not affected by smoking, although smoking is known to change CRP-levels [57].

In addition, elevated titters of non-neutralizing anti-IL-6 AAs have been reported in APS-1, but

Table 3. **Concise overview of characteristics of selected AIAs**

AIAA	Target	Ig type	Action mechanism	Appearance in diseases
Anti-IL-1α	IL-1α	G	N-e	RA, chronic polyarthritis, pemphigus, psoriasis, pustulosis, HS, SLE, IMCD
Anti-IL-1β	IL-1β			HS
Anti-IL-2	IL-2			Type 1 diabetes mellitus, HIV, SLE, HS
Anti-IL-4	IL-4		N. a., may be P-e	N. a.
Anti-IL-6	IL-6		N-e	LC, psychosis, schizophrenia and ID
			P-e	APS-1, systemic sclerosis
Anti-IL-8	IL-8	A, G	S-e	ARDS, ALI, CHP, RA, OC
Anti-IL-10	IL-10	G	N-e	IBD, SLE
Anti-IL-12/23	p35 and p40 subunit	G, M, E		APS-1, thymoma, myasthenia, HS, IMCD and ID
Anti-IL-17	IL-17A, IL-17F	G		APS-1, thymoma, myasthenia gravis, CMC, HS
Anti-IL-22	IL-22			
Anti-IL-33	IL-33	Mainly G		Allergic asthma

Notes. S-e — stimulating effect, N-e — neutralizing effect, P-e — protective effect, N. a. — no data available, RA — rheumatoid arthritis, ARDS — acute respiratory distress syndrome, LC — liver cirrhosis, CHP — chronic generalized periodontitis, OC — ovarian cancer, HS — hidradenitis suppurativa, SLE — systemic lupus erythematosus, IMCD — idiopathic multicentric Castleman`s disease, APS-1 — autoimmune polyendocrine syndrome type 1, CMC — chronic mucocutaneous candidiasis, ALI — acute lung injury.

the clinical significance is not clear yet [77]. However, there is evidence that non-neutralizing anti-IL-6 is a marker of favorable disease course in systemic sclerosis [61, 72].

Other studies report elevated levels of these AAs in patients with schizophrenia, consistent with findings that higher anti-IL-6 titers were found in patients with early stages of psychosis [78].

Anti-IL-6 was also detected in a large cohort of patients with IMCD, most likely due to treatment with siltuximab, so they were excluded from further analysis to prevent result bias; their effect on CRP-levels was not studied [55]. Anti-IL-6 was not detected in HIV-patients with mycoses caused by *Talaromyces marneffei* [79].

Anti-IL-8 AA. Low levels of anti-IL-8 were present in all 15 healthy patients in the study [56], but their pathological role is well described in most patients with ARDS and ALI; when bound to IL-8, they form a stable IL-AA complex that mediates its function through the IgG receptor, FcγRIIa, slowing down spontaneous neutrophil apoptosis and, accordingly, modulating their lifespan, which exacerbates the inflammatory process in the lungs. This is likely mediated by signaling pathways involving the activation of signaling peptides such as: Src, Syk, PI3K/Akt, ERK. The level of those complexes also correlates with susceptibility to the development, severity and mortality of ARDS [80].

Their involvement during CHP (also in refractory form) has been reported [81], and increased levels of free AAs and IL-8 complexes in patients were associated with more severe symptoms in RA with extra-articular manifestations, which allows them to be considered as a marker of this course in the disease [72, 82]. Even earlier studies found that patients with *Helicobacter pylori* infection and active gastritis had excessive expression of anti-IL-8 in the gastric mucosa, which probably plays a role in modulating inflammation [83]. More recent studies have found elevated levels of anti-IL-8 in areas of skin lesions in HS, stage III [68].

In addition, the total concentration of anti-IL-8 IgG was elevated in patients with OC in the early and late stages compared to the healthy controls [84]. This is indirectly confirmed by the data of a subsequent study, which found elevated anti-IL-8 in a large cohort of patients with OC and justifies the use of these AAs as one of a complex of markers for the early diagnosis of OC [84, 85].

Anti-IL-10 AA exhibit IL-10-neutralizing activity in IBD, although the causal relationship between their occurrence and IBD has not been fully established; however, frequent occurrence in healthy individuals has also been reported [56—58, 86]. In terms of clinical action and activity in IBD, they resembled the effects of innate genetic defects, which consisted in the loss of IL-10 functionality or its RC, which blocks normal IL-10 signaling [86]. Tough these AAs are not associated with general autoimmune diathesis, as they were not detected in patients with APS-1 [86, 87] and were also not detected in patients with IMCD [55] and HS, however, IL-10 levels were significantly elevated [67]. They were also detected in a small number of patients with SLE, but did not affect the activity of the disease [66].

Anti-IL-12 and anti-IL-23 AA. Low concentrations of anti-IL-12 have been reported in healthy individuals and in some patients with APS-1. High concentrations of anti-IL-12 AAs have been found in patients with thymoma and myasthenia gravis. It is believed that autoreactive thymic B-cells spontaneously produce AAs against IL-12 or IL-23 in thymoma, and in the case of recurrent thymoma, the neutralizing activity of these ABs increased [64, 72]. It has been shown that immunodeficiency caused by neutralizing AAs to IL-12 can lead to the appearance of multiple abscesses and fistulas, poor wound healing in patients [88].

The presence of IL-12p70 was detected in the serum of patients with stage II HS, and elevated IL-12p70 was found in affected skin areas in stage III [68].

Disruption of IL-12 signaling cascades caused by these AAs leads to a decrease in immune defense against some pathogens [64], which is confirmed by the appearance of anti-IL-12 in several different IDs [61].

IL-12 is known to control Treg-cell homeostasis by eliminating them, particularly during infection with *M. tuberculosis* [6], so it is not surprising that anti-IL-12 AAs have been detected in individual patients with tuberculosis (characterized by severe lung involvement, but can also affect other organs), although it is also associated with IFN AAs [89, 90].

Anti-IL-12 was detected in several patients with IMCD (in three to a separate p40 subunit and in one to IL-12p70) [55]. It is also associated with viral infections; elevated anti-IL-12 titers were also observed in a 26-month-old female patient with Varicella-zoster virus who had RAG-gene deficiency [89, 91], although anti-IL-12 (as well as anti-IL-23) was not detected in HIV-patients with mycoses caused by *T. marneffei* [79]. In addition, one case has been reported in a mature female patient with lymph node inflammation (recurrent lymphadenitis) caused by disseminated infection with *Burkholderia gladioli*, who had not only AAs to IL-12 [92] but also anti-IL-23 [93], which share a common p40 subunit [12].

AAs to IL-23 are also found in patients with thymoma and disseminated, cerebral, and pulmonary ID, and their development depended specifically on the presence of anti-IL-23 AA and positively correlated with neutralization potency [93]. It is interesting that no reactivity of AAs to the p19 subunit was detected [77].

Anti-IL-17 and anti-IL-22 AA. The presence of AAs to IL-17 (A and F) and IL-22 leads to disruption of signaling of these CKs by neutralizing them, resembling genetic disorders. The presence of such AAs has been documented in almost all patients with APS-1 [87] (even in a 7-month-old newborn, although without symptoms until the age of 5 [94]), but they have not been reported in healthy adults [56-58, 88] and are rarely found in people with other ADs, with the exception of thymoma and myasthenia gravis [64]. APS-1 often causes ID such as CMC, in which anti-IL-17/22 was also found in high concentrations, but just the level of IL-17A correlated with the severity of the disease [64, 87].

It appears that the development of AAs to IL-17 causes a disruption of the Th17-response to pathogenic MO, which can even lead to fatal cases, making them an important diagnostic marker [61, 89].

Anti-IL-17 and anti-IL-22 were also detected in several patients with IMCD [55], but anti-IL-17A was not detected in HIV-patients with mycoses caused by *T. marneffei* [79], and there was no statistically significant difference in the detection of anti-IL-17A, anti-IL-17E, and anti-IL-17F in patients with HS compared to controls [67]. However, in more recent studies, elevated levels of anti-IL-17A have been detected in both serum and skin lesions in stage III HS [68].

Anti-IL-33 AA. Currently, data are limited, recently detected in patients with allergic asthma; it is suggested that the conversion of IL-33 to its active form, enhanced by signaling of CKs, responsible for B-cell activation, and TLR9, with reduced Treg-cell function, may induce the development of AAs to IL-33 in the periphery. Further *in vitro* and *in vivo* experiments showed that AAs administration reduced induced inflammation. This allows these AAs to be considered as a possible therapeutic agent for asthma, because this is clinically associated with improved airway function and the amelioration of symptoms [95].

Discussion

ILs play a central role in the immune system signaling events. By interacting with their Rs, they initiate signaling cascades that affect the immune response in various ways. Disruption of this signaling can be caused by some natural AAs [2]. AIAs are getting more attention because they can exert a distinctive effect on the functionality of these molecules by stimulating or, conversely, blocking their binding to their Rs. Although their occurrence is mostly associated with reduced immune tolerance [52, 95], the proposed concept of adaptive tolerance [52, 53], the role of certain AIAs as markers of favorable disease progression in some diseases [64, 65, 72, 95], as well as convincing data from recent studies that were detected them in a significant

number of healthy individuals (however not all types) (Tabl. 2) [56—58] suggest that the presence of some AIAs (both pro- and anti-inflammatory ILs) is an additional regulatory mechanism that maintains homeostasis by modulating IL-levels in the body. However, under physiological conditions, AIAs are found in relatively small amounts [56—58] that do not disrupt IL-mediated signaling, whereas in pathological processes, AIAs-levels increase significantly as in the case of neutralizing anti-IL-6 and low CRP-levels (a classic marker of the inflammatory process) [73—76], which can be explained by the effect on the IL-6-gp130-JAK-STAT3-CRP signaling axis [36, 75] and, apparently, actually increases susceptibility to infections. On the other hand, IL-6 has been shown to play a minor role in stimulating the Th-17 response in *M. tuberculosis* infection, but in streptococcal infection, its presence played a decisive role [96].

AAs to p40-ILs also increase patient's susceptibility to infections, with a key role being attributed to anti-IL-23 rather than anti-IL-12, as previously thought, and resembling the defects caused by IL-12R deficiency [93], extending the view of the effect of ACAs to be comparable to that of congenital genetic disorders [54].

Despite the infrequent detection of anti-IL-17 and anti-IL-22 in several recent studies in patients with other AD [55, 64, 68], they remain an important diagnostic marker in APS-1 and are also likely to be the cause of CMC in such patients [61, 87, 94] The elevated levels of protective anti-IL-6 in APS-1 in some patients may be an effort of the body to normalize the Th17-response [77], which may be mediated by IL-6 in other diseases [36], although preliminary data did not detect them in patients with APS-1 [87].

Focusing on the detection of anti-IL-23 and anti-IL-17 may be a strategy for establishing the etiology of severe ID when other diagnostic approaches fail to provide answers, which may contribute to more effective therapy [97].

On the other hand, there are no data on a possible role of anti-IL-33 AA in the course of ID (it is well known that IL-33 plays an important role in counteracting pathogenic microorganisms [20, 25, 26]), particularly in relation to respiratory diseases, although a favorable effect in asthma has been described [95], which is similar to the effect of recently described monoclonal ABs to IL-33 [98]. Interestingly, anti-IL-17 also protects the APS-1 patients from asthma [99] and modified (antagonistic) IL-17F helped protect Japanese patients from both asthma and chronic obstructive pulmonary disease (COPD) [100], and as we know, the pathogenesis of COPD remains unclear. However, it has been shown *in vivo* that during the induction of COPD by *Edwardsiella tarda*, there was increased expression of IL-33 in lung tissues, which triggered an autoimmune reaction with the production of Ig G AAs, but their action was directed against alveolar EpCs-proteins and elastin fragments, and the appearance of AIAs has not been studied [101].

In addition, IL-33 stimulates IL-8 secretion via the ST2R-ERK pathway, which may also exacerbate airway inflammation in asthma [102]. The role of anti-IL-8 in the course of asthma has not been described in recent studies [95], however, they enhance IL-8 activity in ARDS [80], which often occurs as a result of ID, and although an increase in the level of these AAs associated with infection (*H. pylori*) has been previously reported [83], a possible role of AIAs in the course of infectious ARDS has not been established.

Conclusion

Despite the detection of AIAs in significant cohorts of healthy individuals, we support the view that their occurrence is certainly an important factor in the course of various diseases, which can have either negative or positive consequences, and we also identified several potential directions for further experimental research, with a focus on respiratory diseases.

The AIAs-focused studies open new perspectives for understanding the pathogenesis of different AD, ID, and ChD, as well as for developing new possible approaches to effective, targeted and tailored therapy.

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ІНТЕРЛЕЙКІНИ ТА АНТИ-ІНТЕРЛЕЙКІНОВІ
АУТОАНТИТІЛА В НОРМІ ТА ПРИ ПАТОЛОГІЇ

Анти-інтерлейкінові аутоантитіла (AIA) — це особливий тип імуноглобулінів, які націлені проти власних інтерлейкінів (IL) організму, що є ключовими білковими медіаторами імунної системи. Попри те, що присутність AIA здебільшого асоціюється із рядом різних імунодефіцитних станів, останні дослідження демонструють, що їх наявність у здорових людей є варіантом норми, хоча і у невеликих кількостях. До того ж підвищення їх титрів може також бути маркером сприятливого прогнозу або навіть зменшувати тяжкість перебігу деяких захворювань. Дослідження AIA відкриває нові перспективи для розуміння патогенезу аутоімунних і інфекційних захворювань, а також розроблення нових підходів ефективної та націленої терапії.

***Ключові слова*:** інтерлейкіни, анті-цитокінові аутоантитіла, анти-інтерлейкінові аутоантитіла, ревматоїдний артрит, гострий респіраторний дистрес-синдром, астма, аутоімунний поліендокринний синдром 1го типу.