Cytokines regulate a wide range of physiological processes during development of the normal immune response, and they are involved in the pathogenesis of autoimmune diseases. Disorders in pro- and anti-inflammatory cytokines’ balance and recognizing self tissues as foreign by the immune system cells can trigger the development of autoimmune pathologies. Anti-cytokine therapy alone or combined with different classes of immunosuppressive drugs has been shown to be highly effective. Some cytokines have been shown to be good therapeutic targets for treatment of autoimmune and inflammatory diseases. A great number of anti-cytokine drugs are already successfully used in clinical practice, and more biologics are under development. In the present review, we consider the biological effects of three main pro-inflammatory cytokines: TNF (tumor necrosis factor), IL-1 (interleukin 1), and IL-6 (interleukin 6), as well as the action mechanisms of their inhibitors.

**TNF AND ITS BIOLOGICAL EFFECTS**

Tumor necrosis factor (TNF-α) was discovered in 1975 in L. Old’s laboratory as a specific product of lymphocytes and macrophages that induces lysis of definite type cells including tumor cells [1]. TNF became the “founder” of a whole family of homologous cytokines: LTA, CD40L, CD27L, FASL, etc. These cytokines transmit a signal through TNF family receptors (TNFR), which include such molecules as the FAS receptor (CD95, Apo-1) and the co-stimulatory receptor CD40. TNF is able to bind with two receptors of this family: TNFR1 and TNFR2 (Fig. 1a). TNFR1 (p55) is present on the membrane of various cells, whereas TNFR2 (p75) is mainly expressed by immunocytes and endothelial cells [2].

There are two forms of TNF and both are active as homotrimers: the membrane-bound one consisting of 26-kDa monomers and the soluble one consisting of 17-kDa monomers. Transmembrane TNF (mTNF) gives rise to the soluble form (sTNF) due to a specific cleavage of the polypeptide chain between amino acid residues 76 and 77...
The majority of proinflammatory functions of mTNF and sTNF are mediated through binding with TNFR1 and the downstream activation of transcription factors of the NF-κB and AP families, which, in turn, trigger the expression of the other proinflammatory cytokines including IL-1 and IL-6 [4]. The role of TNFR2 is not studied in detail, but the binding of mTNF to TNFR2 has been shown to contribute to the regulation of T-cell migration, proliferation, activation, antigen presentation, tissue repair, and angiogenesis [5-7]. During the development of inflammation, signal transduction through TNFR2 is necessary to stabilize the regulatory T-cell pool and prevent damage of self tissues [8].

The extracellular domains of TNFR1 and TNFR2 also can be shed under the influence of proteolytic enzymes and thus produce soluble forms of the receptors [9, 10]. For example, the soluble form of TNFR2 performs an immunoregulatory function and participates in pathogenesis of *M. tuberculosis* infection in mice [11].
The role of TNF in the development of inflammation is studied extensively. For instance, during pathogenesis of rheumatoid arthritis (RA), TNF stimulates endothelial cells to express integrins and adhesion molecules. TNF also induces the production and secretion of such chemokines as CXCL8, CCL2, and CCL5. The combination of these signals leads to extravasation of leukocytes and their subsequent accumulation in the site of inflammation. Moreover, TNF induces the differentiation of monocytes. The infiltrating, activated leukocytes in turn produce proinflammatory cytokines IL-1, IL-6, and TNF and thus provide a positive feedback regulation and promote inflammation. Furthermore, TNF activates synovial fibroblasts, which form an inflammatory pannus and destroy cartilage. Finally, TNF directly stimulates osteoclasts, which are responsible for resorption of bone tissue [12].

However, negative feedback mechanisms are also involved in these processes: signaling through TNFR2 suppresses osteoclastogenesis, and the transmembrane form of TNF acts as antagonist of osteoclast activation [13].

TNF INHIBITORS IN THERAPY OF RHEUMATOID ARTHRITIS AND OTHER AUTOIMMUNE DISEASES

Clinical trials of TNF inhibitors have shown for the first time that inhibition of only one cytokine can break the vicious cycle of immune system activation, gain effective control of pathological inflammation symptoms, ameliorate deceleration of joint destruction, and in some cases can cause in patients a stable remission even after abolishing the anti-TNF therapy [14-17].

At present, TNF inhibitors are successfully used in the treatment of many autoimmune diseases. In the majority of developed countries, application of five different TNF inhibitors is approved (Fig. 1b and table). Infliximab was the first TNF inhibitor found useful for the treatment of patients with Crohn’s disease unresponsive to the conventional therapy [18, 19] and for the treatment of RA. Later, infliximab was shown to be effective also for the therapy of ankylosing spondyloarthritis [20, 21] and psoriasis [22].

Infliximab is a chimeric monoclonal antibody with constant regions of human IgG1 and variable domains of light and heavy chains of mouse origin. This antibody is highly specific and has a high affinity for both human sTNF (monomer and trimer) and human mTNF [23]. Its effects include suppression of cell migration, of infiltration of the synovial membrane, and of activation of leukocytes (including macrophages). Infliximab diminishes angiogenesis and osteoclastogenesis, which prevents damage to the bone tissue. Infliximab can induce lysis of cells carrying mTNF on their surface [24], i.e. participates in the antibody-dependent cellular and complement-mediated cytotoxicity.

Etanercept is another TNF inhibitor approved for the treatment of RA. Etanercept is a fusion protein consisting of the dimer of the extracellular TNF-binding domain of human TNFR2 bound with the Fc-fragment of human IgG1. Unlike the other inhibitors, etanercept inhibits lymphotoxin-α (LTα) as well as TNF. Physiological functions of this TNF-like cytokine are not yet studied in detail. However, LTα was recently shown to control IgA production in the intestine and influence the composition of intestinal microbiota independently of TNF and lymphotoxin-β [25]. Considering that etanercept, in contrast to infliximab, is inefficient in inflammatory intestinal diseases (including Crohn’s disease), this problem needs to be studied further. However, etanercept was shown to be effective in the treatment of ankylosing spondyloarthritis and psoriasis.

Later, adalimumab was also found useful for the treatment of patients with RA. Adalimumab is an antibody capable of binding and neutralizing human TNF (both the membrane-bound and soluble forms) that was prepared using a phage display method from the library of V_L and V_H fragments of human IgG1 [26, 27]. Adalimumab is now also used in the therapy of ankylosing spondyloarthritis, Crohn’s disease, and psoriasis.

In addition to the above-listed agents, two other TNF inhibitors are also approved: certolizumab pegol and golimumab [28]. Certolizumab pegol is a recombinant humanized Fab’-fragment specific to human TNF (hTNF) conjugated with a polyethylene glycol molecule of 40-kDa size [29] that ensures prolonged lifetime of the agents in the body. Because this inhibitor lacks the Fc-fragment, it cannot induce antibody-dependent cytotoxicity.

Golimumab is a monoclonal antibody against hTNF with a full human amino acid sequence that is already approved for the treatment of arthritis and ankylosing spondyloarthritis. This antibody was prepared using a unique technology in transgenic mice with the human immunoglobulin locus. Golimumab has the highest affinity for TNF among all inhibitors now used in clinical practice [30]. Due to absence of mouse antibody fragments, the immunogenicity of adalimumab and golimumab is lower than the immunogenicity of the chimeric antibody infliximab.

It should be noted that notwithstanding the about 20-year history of studies, the action mechanisms of anti-TNF preparations are still not well understood. Thus, it has been found only recently that inhibition of TNF mediated through non-immune mechanisms can lower pain in an inflamed joint, which is important in the treatment of arthritis [31]. In the collagen-induced model of arthritis in mice, it has been shown that inhibition of TNF leads, on one hand, to activation of Th1/Th17 cells, but, on the other hand, prevents their migration from lymph nodes into the inflammation locus [32]. Recent studies with RA patients also demonstrated that long-term anti-TNF therapy caused a decrease in the number of Th17 cells in joints.
Moreover, therapy with TNF inhibitors induced pro-
duction of Th17 cells, which produced IL-10 [34], inhib-
ited the dev elopment of germinal centers, decreased the
number of memory B-cells [35], and restored the balance
of regulatory T-cells [36, 37]. Notably, the list of potential
complications associated with such therapy is increasing
because TNF is involved in many physiological functions,
and in some of them its role is unique.

IL-1 AND REGULATION OF ITS FUNCTIONS

Interleukin-1 (IL-1) was one of the first interleukins
identified due to its biological activity [38]. Its molecular
structure was determined in the middle 1980s, and there-
after some members of the IL-1 family were described
and their important role in the development of the
immune response was discovered.

IL-1 is represented by two proteins, IL-1α and IL-
1β, which are encoded by two related genes, \textit{IL1A} and
\textit{IL1B}. In addition to IL-1α and IL-1β, the family of IL-1
cytokines includes also the proinflammatory cytokine IL-
18 and an antagonist of the IL-1 receptor (IL-1Ra) that
has an anti-inflammatory action [39]. Recently, six new
cytokines of this family have been described (from IL-1F5
to IL-1F10) [40-42]. Cytokines of the IL-1 family play an
important role in immune response regulation and in the
development of inflammation through the control of
expression of many effector proteins, such as cytokines,
chemokines, cytoplasmic metalloproteinases, etc. [43].

A signal from IL-1 cytokine family is transduced via
a group of related receptors. These receptors contain in
the cytoplasm an extracellular immunoglobulin domain
and the Toll/IL-1 (TIR) receptor domain. In the case of
IL-1α/β, the ligand initially binds to the primary subunit
of the receptor (IL-1R1), and then the second subunit of
the receptor (IL-1RAcP) binds to this complex (Fig. 2a).
Formation of the heterodimer allows the TIR domain to
bind the adaptor protein MyD88. The binding of MyD88
to the receptor heterodimer recruits signaling kinases

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<th>Name</th>
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Notes: CD, Crohn’s disease; UC, ulcerative colitis; RA, rheumatoid arthritis; AS, ankylosing spondyloarthritis; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; Ps, psoriasis.
IRAK1 and IRAK4. IRAK4 activates IRAK1, then the IRAK1–IRAK4 complex triggers a signaling cascade that results in the activation of the NF-κB and MAPK pathways [44, 45].

Although IL-1α and IL-1β use a common receptor for signaling, their effects are different. IL-1α is produced by the majority of cells of healthy humans. It is synthesized as a precursor associated with cytoskeleton elements (microtubules) mainly localized within the cell. Upon release from the cell, IL-1α acts locally. IL-1β cannot be detected in blood sera of healthy humans by standard tests. Components of the complement system, hypoxia, and blood coagulation can induce the transcription of IL-1β mRNA, but this is virtually not accompanied by translation of IL-1β because additional stimulation is necessary to initiate translation. Such stimulation can be carried out by both proteins of bacterial cells and by cytokines (TNF, IL-18, IL-1α) including IL-1β [43, 46]. In the presence of these factors, monocytes, macrophages, and dendritic cells produce IL-1β that circulates systemically.

The biological activity of IL-1 is strictly regulated at several levels. For activation of IL-1β, its precursor has to be processed by an intracellular proteinase — caspase 1. This proteinase, in turn, is activated on oligomerization of an intracellular complex of proteins that is called the “inflammasome” [47].

Earlier IL-1α was believed to be an endogenous signal of danger passively released during cell death. However, recently it was shown that the secretion of both IL-1α and IL-1β could be activated by the inflammasome both in vitro and in vivo [48].

When the active forms of these cytokines are released, their action can be downregulated through two pathways. First, IL-1RA can bind to the IL-1R1 receptor and thus prevent its binding with IL-1α and IL-1β. Moreover, the binding of IL-1RA with the receptor does not initiate signal transduction because no binding with IL-1RACp occurs [39]. Second, the extracellular region of the second type IL-1 receptor (IL-1R2) is homologous to the IL-1R1 domain, but its short cytoplasmic domain is unable to transmit the intracellular signal. Thus, IL-1R2 acts as a decoy receptor, and it is supposed that its main role is to exclude excess of autocrine activation of the IL-1 signal [49, 50]. IL-1R2 can also be shed from the cell surface, and as a soluble protein it inhibits ligand binding with the receptor [51]. Finally, there is a soluble form IL-1RACp that binds with soluble IL-1R2 and thus increasing its inhibitory activity [44, 52, 53].

ROLE OF IL-1 IN DEVELOPMENT OF CHRONIC INFLAMMATORY DISEASES AND THERAPEUTIC INHIBITORS

Disorders in the regulation of synthesis and secretion of IL-1α/β can lead to serious pathologies. Many “classic” chronic inflammatory diseases are associated with increased level of IL-1α/β caused by constant activation of its synthesis and secretion due to activation of inflammasomes.

Note that cryopyrin-associated periodic syndrome is characterized by appearance of a mutation in a component of the inflammasome, cryopyrin, which stimulates the activity of caspase 1 and therefore leads to an increase in IL-1β secretion. Other chronic inflammatory diseases (gout, multiple sclerosis, hypertension) are characterized by hyperuricemia. Uric acid produces urate crystals that activate inflammasomes and also result in chronic inflammation mediated through IL-1. In type-2 diabetes, elevated glucose concentration increases the metabolic activity of Langerhans islets that leads to an increase in the concentration of reactive oxygen species and activation of the inflammasome. Moreover, the increase in glucose concentration stimulates the production of insulin, which induces stress of the endoplasmic reticulum that, in turn, activates the inflammasome. Altogether, this results in a closed cycle where the activation of the IL-1β pathway is stimulated by a positive feedback mechanism. Moreover, β-cells can produce an amyloid polypeptide that also activates synthesis of IL-1β through the inflammasome. Thus, the increased production of IL-1β can result in the loss of β-cells of the pancreas [54].

In the therapy of these chronic inflammatory diseases, the IL-1 inhibitors (anakinra, rilonacept, and canakinumab) are actively used [55-57]. These inhibitors block signal transduction through IL-1/IL-1R and thus interrupt the closed circle of inflammation.

Anakinra is a non-glycosylated recombinant soluble antagonist of the IL-1 receptor (IL-1RA) that differs from human IL-1RA by presence of an additional methionine. By binding to the IL-1 receptor, anakinra inhibits effects of both IL-1α and IL-1β. Rilonacept (IL-1 TRAP) is a recombinant dimeric chimeric protein consisting of extracellular domains of human proteins IL-1R1 and IL-1RACp joined with the Fc-fragment of human IgG. This protein can bind with IL-1α/β and inhibit their functions. Canakinumab is a humanized monoclonal antibody against IL-1β (Fig. 2b and table).

Similarly to TNF, IL-1 is a key mediator of pathological processes in tissues during RA [58]. IL-1β is secreted by macrophages, T-cells, fibroblasts, and chondrocytes of the synovial membrane, and its level is elevated in the synovial fluid of patients with RA [52, 59]. Along with TNF, IL-1 induces expression and production of some chemokines (CXCL12, MIP-1α, RANTES, and MCP-3) and adhesion molecules (VCAM-1, E-selectin, and ICAM-1) that bind to receptors on the surface of leukocytes and thus promote their penetration into the synovial membrane [60-62]. It seems that IL-1 can contribute to the development of RA through stimulating synovial fibroblasts to produce some cytokines, such as IL-15 and IL-18. In turn, IL-15 activates T-cells, macrophages
(including TNF production), and fibroblasts of the synovial membrane. IL-18 promotes increase in IL-1 and TNF concentration by a positive feedback mechanism and also influences migration of T-cells and promotes angiogenesis [63]. Moreover, IL-1 lowers synthesis of intercellular matrix molecules, in particular, of proteoglycans in cartilaginous tissue [64], and introduction of the IL-1 receptor inhibits this effect [65]. Recently IL-1β was shown to induce proliferation of Th17 cells together with TGF-β, and on administration of anakinra the number of Th17 cells was significantly decreased, which correlated with a remission of patients with RA [66].

Clinical trial has shown that in RA anakinra abolishes the inflammation and reduces bone destruction, but...
these effects are weaker than effects of TNF inhibitors [67]. Neither TNF inhibitors nor anakinra are effective in sepsis [68, 69]. This might be because pathogenesis of RA and sepsis is associated not only with deregulation of the classical pathway of inflammation, but also with dysfunction of T-lymphocytes and humoral immune response [55]. However, in such diseases as gout and type-2 diabetes, therapy with IL-1 inhibitors is extremely efficient, whereas treatment with TNF antagonists is not only ineffective, but it can even aggravate the symptoms.

MECHANISMS OF SIGNALING AND PHYSIOLOGICAL FUNCTIONS OF IL-6

IL-6 was discovered simultaneously in several laboratories and was initially known under different names, including interferon-β2. The cDNA of IL-6 was first cloned and expressed in 1986 [70].

IL-6 is a protein with length of 184 amino acids that forms a bundle of four antiparallel helices. It is a member of the cytokine family with similar three-dimensional structure [71]. The family includes IL-11, IL-27, IL-31, ciliary neurotrophic factor (CNTF), cardiotrophin-like cytokine (NNT-1), cardiotropin-1 (CT-1), neuropoietin, and oncostatin M [72] that contribute to the regulation of inflammation via the control of differentiation, proliferation, migration, and apoptosis of target cells. This cytokine family is characterized by signal transduction through the transmembrane protein gp130 (CD130), which is a common subunit of receptors of these cytokines.

The binding of IL-6 to the receptor causes dimerization of gp130, which leads to activation of tyrosine kinases of the JAK family. Activated JAKs, in turn, phosphorylate and activate transcription factors of the STAT family, e.g. STAT3 in the case of the IL-6 receptor [73, 74].

Note that the signal from IL-6 can be transmitted through both the “classical” mechanism and an alternative mechanism, so-called “trans-signaling”. In the classical pathway of signal transduction, IL-6 binds to the membrane-bound receptor of IL-6 (IL-6R), which induces association of this complex with the gp130 homodimer that then transmits the signal into the cell (Fig. 3a). Because IL-6R is expressed by limited cell types (hepatocytes, neutrophils, monocytes, macrophages, glia cells, neurons, and some lymphocytes), the influence of IL-6 is expected to be limited. On the other hand, it was known that IL-6 acts also on other cells. It occurred that during the proteolytic processing (shedding) of membrane-bound IL-6R by metalloproteinases ADAM10 and ADAM17 [71, 75], a soluble form of the IL-6 receptor (sIL-6R) can be produced. It seems that neutrophils [76], macrophages [77], and CD4+ lymphocytes [78] infiltrating inflamed tissue can be a source of sIL-6R. Moreover, sIL-6R can be produced also during alternative splicing of IL-6R mRNA. It is important that, unlike other soluble receptors (e.g. sTNFR), sIL-6R has features of an agonist and in complex with IL-6 can activate target cells if a sufficient number of protein gp130 molecules is present on their surface. Thus, even cells not expressing IL-6R on their surface can receive via sIL-R6 a signal from IL-6 due to “trans-signaling”, which increases the number of potential target cells for IL-6. Trans-signaling, in turn, can be inhibited by a soluble form of the gp130 protein (sgp130) that is produced by an alternative splicing of gp130 mRNA.

It was already noted that IL-6 was initially described as a factor of B-cell differentiation inducing their maturation to plasma cells [70]. At present, IL-6 is discovered to be a regulator of many other functions of both immune and non-immune cells and to be a connecting link between the immune, nervous, and endocrine systems. This cytokine influences the differentiation and growth of T-cells, activation of NK cells, maturation of megakaryocytes, development of osteoblasts, and synthesis of acute phase proteins in hepatocytes [79, 80]. IL-6 acts as a growth factor for myelomas, keratinocytes, mesangial cells, renal carcinoma, and Kaposi sarcoma cells and stimulates the growth of hemopoietic stem cells [81, 82]. Moreover, IL-6 is essential for normal functioning of the brain; it is involved in the control of energy consumption and of pituitary–adrenal axis stimulation [83-85]. The role of IL-6 in blocking pain symptoms, regulation of sleep–wake cycles, emotional reactivity, and also in behavioral effects including learning and memory was described in IL-6-deficient mice (see review [86]).

Dysfunction of the regulatory network connected with this cytokine can lead to chronic and acute inflammations, autoimmune diseases, and neoplastic disorders. IL-6-deficient mice are resistant to development of collagen- and antigen-induced arthritis, indicating that IL-6 plays a key role in the development of chronic inflammation and autoimmune diseases [87].

THERAPEUTIC INHIBITION OF IL-6

For the defense of the body against such stresses as infections and traumas, IL-6 triggers a wide range of signaling events. When the “danger” disappears, the activation regulated by IL-6 is suppressed through a negative feedback system that normalizes the IL-6 level. However, the uncontrolled production of IL-6 can shift the balance to the Th17/Th1 side with reduction of regulatory T-cells (Treg) and can cause various autoimmune and chronic inflammatory diseases. It was shown in mouse models that IL-6 inhibition suppressed the differentiation of Th17/Th1 cells simultaneously with activation of Treg [88, 89]. Causes of IL-6 deregulation in vivo are not fully understood and are still being intensively studied.
Fig. 3. Action mechanism of IL-6 inhibitors. a) Structure of the ligand–receptor system for IL-6. The transmembrane form of IL-6R that binds IL-6 is represented in complex with two molecules of gp130. To the right: inhibition of IL-6 or IL-6R by monoclonal antibodies, as well as the capture of IL-6 by the soluble form of IL-6R in complex with recombinant soluble gp130-Fc prevents the activation of gp130 and subsequent transduction of the signal. b) Schematic figures of IL-6 inhibitors.
It has been said already that IL-6 plays a key role in the development of collagen- and antigen-induced arthritis; moreover, overproduction of IL-6 in transgenic mice is associated with the development in them of a syndrome similar to Castleman disease, and the symptoms of inflammation decrease upon IL-6 blockade. These data and others have become a reasonable basis for anti-IL-6 therapy in chronic systemic inflammatory diseases.

Tocilizumab was the first inhibitor of IL-6 approved for clinical application. It is a humanized monoclonal antibody to the IL-6 receptor (Fig. 3b and table). This antibody inhibits IL-6 due to binding with both IL-6R and sIL-6R. Tocilizumab was shown to improve the Th17/Treg balance in rheumatoid arthritis [90] and to normalize the blood serum level of amyloid A [91]. Roll et al. [92] found that tocilizumab restores the numbers of peripheral memory B-cells in patients with RA. Moreover, anti-IL-6 therapy was shown to induce the production of CD39+ Treg in a collagen-induced mouse model of RA [93]. Finally, therapy with tocilizumab decreased the number of pathologic CD38<sup>high</sup>/CD19<sup>low</sup>IgD<sup>neg</sup> plasma cells in patients with systemic lupus erythematosus and decreased the survival of plasmablasts. Together, these data suggest that the positive clinical effect of tocilizumab may be partially due to inhibition of production of pathologic autoantibodies.

Tanaka et al. [94] compared the efficiency of tocilizumab with that of TNF inhibitors and concluded that their efficiencies were comparable if tocilizumab was used in combination with methotrexate. However, during monotherapy it is preferable to use tocilizumab. Moreover, in some cases patients who did not respond to therapy with TNF inhibitors reacted positively to treatment with tocilizumab. On the other hand, TNF inhibitors seem to be more effective in the treatment of ankylosing spondyloarthritis and inflammatory diseases of the intestine [88].

The successful clinical application of tocilizumab stimulated the development of other inhibitors of IL-6 (table). Data are now published on the second phase of clinical trial of such therapeutic antibodies as olokizumab, sarilumab, clazakizumab, and sirukumab [95].

Olokizumab and clazakizumab are humanized monoclonal antibodies capable of binding and neutralizing IL-6, whereas sarilumab and sirukumab are monoclonal antibodies against IL-6R. Sarilumab and sirukumab interact with both the membrane-bound and soluble IL-6 receptor, whereas anti-IL-6 antibodies bind with IL-6 and thus inhibit its binding with the receptors. All these therapeutic agents display similar clinical effects, and the efficiency and safety of these four new inhibitors of IL-6 are similar to those parameters of tocilizumab.

Still more data have been published recently showing that the IL-6 “trans-signaling” transmits signals about local and transient damage in the body but is poorly acting at the absence of stress conditions, whereas the classical pathway of signal transduction is responsible for maintaining homeostasis. Under pathological conditions, the levels of IL-6 and sIL-6R in the body are noticeably increased [96]. An important function of the IL-6 trans-signaling is to control the adaptive immunity including the differentiation of Th17 cells that are involved in the development of chronic inflammatory diseases, suppression of Treg proliferation, and the attraction of lymphocytes and neutrophils into an inflamed joint in arthritis. After extensive studies on the role and functions of the IL-6 trans-signaling, a chimeric protein sgp130Fc was constructed [87] consisting of an extracellular (soluble) domain of human gp130 protein and the Fc-fragment of human IgG1 (Fig. 3b). This protein can bind with the IL-6–sIL-6R complex but does not bind with sIL-6R. Thus, the protein sgp130Fc selectively inhibits the transduction of the IL-6 signal by “trans-signaling” without a noticeable effect on the classical pathway [97]. Injection of sgp130Fc into mice increased survival in the model of polymicrobial sepsis [98], reduced symptoms of collagen-induced arthritis [99], and lowered inflammation in Crohn's disease, acute colitis, and systemic intestinal diseases [97, 100]. Now the IL-6 inhibitor based on the sgp130Fc protein is under clinical trial [87].

**CONCLUSION**

The introduction of anti-cytokine therapy in clinical practice for chronic inflammatory diseases has made a real revolution in medicine. However, such therapy affecting fundamental protective functions of the body mediated through particular cytokines has some limitations.

For instance, TNF is necessary for maintaining the integrity of granulomas on infection with intracellular pathogens such as *Mycobacterium* and *Listeria*; therefore, using TNF inhibitors is associated with an increased risk of development of latent opportunistic microbial infections [101]. There is a risk of activation of latent tuberculosis infection on treatment with tocilizumab; however, up to now no case of reactivation of tuberculosis has been described during treatment with anakinra [102].

Cases of demyelization were described during long-term therapy with TNF inhibitors, although it was believed that a systemically injected inhibitor could not penetrate across the blood–brain barrier. Studies on mice have shown that chronic inhibition of TNF action increases antigen-specific T-cellular response that can lead to survival of peripheral autoreactive myelin-specific T-cells. Moreover, suppression of TNF function through feedback mechanisms results in decrease in IL-10 secretion and consequently in increase in IL-12 and INFγ secretion that is specific for multiple sclerosis and leads to demyelination [103].

The use of TNF inhibitors can lead to development of secondary autoimmune manifestations. Thus, binding
of TNF inhibitors with the transmembrane TNF can result in the cell apoptosis, release of nuclear antigens, and production of autoantibodies. In some cases inhibition of TNF can lead even to appearance of symptoms of lupus erythematosus. Moreover, inhibition of TNF is associated with an abundant secretion of interferon that, in turn, can result in thromboembolism. Concurrent infection can trigger these processes, as a result of inhibition of TNF [104].

New therapeutic blockers of all three main proinflammatory cytokines that would minimize adverse effects while maintaining the efficiency of current drugs are currently developing. In particular, studies on mouse models have shown that TNF secreted by particular cell sources would display better therapeutic effect if it did not affect the protective functions of TNF. Similarly to TNF, IL-6 also has a dual nature, but this is partially associated with different pathways of signal transduction. An inhibitor of IL-6 capable of interrupting the signal transduction only through trans-signaling [87] that is responsible for pathological effects of IL-6 is now already under the first phase of clinical trial. On the application of the first inhibitors of IL-1, the main side effect was inflammation at the injection site, partially caused by the need for frequent injections of the first inhibitor, anakinra, which had a short half-life (4–6 h) [55]. Inhibitors of the new generation (e.g. canakinumab) have a significantly more prolonged half-life.

The anti-cytokine therapy already actively used in various countries is based on comprehension of molecular mechanisms of pathological processes associated with expression of cytokines and undoubtedly will remain an innovative trend in clinical medicine for many years.

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