

Clinical significance of interleukin-6 (IL-6) as a prognostic factor of cancer disease

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Abstract: Interleukin-6 (IL-6) is proinflammatory cytokine that produces multifunctional effects. It is also involved in the regulation of immune reactions, hematopoiesis and inflammatory state. Interleukin-6 has been shown to be associated with tumor progression including inhibition of cancer cells apoptosis and stimulation of angiogenesis. Anti-IL-6 therapy is a new strategy in the inflammatory autoimmune diseases and cancer. Clinical studies have shown elevated serum IL-6 concentrations in patients with endometrial cancer, non-small cell lung carcinoma, colorectal cancer, renal cell carcinoma, breast and ovarian cancer. Serum IL-6 levels correlate with tumor stage, and survival of patients. In this article we have focused on a role of IL-6 as a prognostic factor in several malignancies such as colorectal cancer, breast cancer, gastric cancer and pancreatic cancer.

Key words: cancer, interleukin-6

INTRODUCTION

Cytokines regulate functions of many cells conditioning their interaction by activation or inhibition [1]. One of the cytokine groups are interleukins including interleukin-6 (IL-6), a glycoprotein of a molecular weight of 26 kDa, composed of 184 amino acids [2]. Because of its multiple activities, it has been suggested that IL-6 is the main factor involved in host response to a foreign pathogen. Interleukin-6 which plays a major role in immunologic response, hematopoiesis and inflammation [3,4] was also termed a β -cell stimulatory factor, β_2 -interferon, a hybridoma growth factor, or a cytotoxic T cell differentiation growth factor. IL-6 has a similar structure to the factor which stimulates hepatocytes to the synthesis of acute-phase proteins [2].

The human gene for IL-6 is located on 7p15-p21 chromosome and has the structure similar to the gene for granulocyte colony-stimulating factor, which explains the functional similarity of both cytokines [5,6].

Interleukin-6 acts on the cells using receptor type I, the type of hematopoietic cytokine receptor which belongs to gp130 [5] and is expressed on lymphoid and nonlymphoid cells. The IL-6 receptor consists of different α chains (80 kDa) and identical β chains (130 kDa) transmitting signals into cells [5,6]. There are two types of receptors for IL-6: the IL-6R with low affinity, which after binding with IL-6 forms the complex with gp130 and activates tyrosine kinase, and the soluble

interleukin-6 receptor binding with IL-6 and then with the membrane receptor β chain – gp130, which leads to the intracellular signal [5,7,8].

Biological activity

Interleukin-6 is produced mainly by monocytes and macrophages and in a smaller percentage by fibroblasts, endothelial cells, lymphocytes T and B, chondrocytes and amnion cells. The production of interleukin-6 is stimulated by interleukin-1 (IL-1) and interferon (INF), tumor necrosis factor (TNF), lipopolysaccharide, DNA viruses and RNA viruses [5].

Interleukin-6 is a multifunctional cytokine with pleiotropic effects (Fig). Its importance lies in the stimulation of lymphocytes B differentiation and induction of permanent differentiation of lymphocytes B into plasma cells which produce different classes of immunoglobulin. Interleukin-6 stimulates lymphocytes T to the production of interleukin-2 (IL-2) and the synthesis of its receptors. Both IL-6 and IL-1 also activate lymphocytes T which recognize antigens, and stimulate the proliferation and differentiation of cytotoxic lymphocytes in the presence of IL-2. Moreover, it can induce both activated and resting lymphocytes [5]. Interleukin-6 responsible for lymphocytes T activation is released by monocytes [6]. Interleukin-6 together with IL-3 activate the proliferation and differentiation of early progenitor cells, first of all megakaryocytic progenitors [5], but also erythroid and granulocyte-macrophage progenitors [6]. Interleukin-6 has a direct effect on megakaryocytes using specific receptors and also, similar to thrombopoietin, mediates the synthesis of platelets [9]. Interleukin-6 stimulates keratinocytes outgrowth, induces the proliferation of neurons and increases the production of the vascular endothelial growth factor [3,10]. It is one of the cytokines belonging to so-called positive growth

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regulators, which along with the granulocyte-macrophage colony-stimulating factor, the granulocyte-colony stimulating factor, IL-1 and IL-3 stimulate the proliferation and differentiation of myeloid cells and their apoptosis [6]. Because the role of this proinflammatory cytokine in activation and differentiation of lymphocytes Tc and NK is well known, the pathway of anti-cancer effects of IL-6 was used in the cancer therapy. Ullmann et al. [11] reported that IL-6 increases overexpression of carcinoembryonic antigen (CEA) and antigens HLA class I on the surface of colorectal cancer cells. The trials were conducted using IL-6 for direct inhibition of cancer cell proliferation. Unfortunately, in some solid tumors, IL-6 can be an autocrine and paracrine growth stimulus, for example, in breast carcinoma, melanoma, urinary bladder cancer and prostate cancer [5].

The role of IL-6 in inflammation and infection

Serum IL-6 levels may increase even 100-fold in inflammation, and therefore this cytokine has been proposed as an early and sensitive but not specific marker for inflammatory reaction. It is a major stimulus for the synthesis of acute-phase proteins in the liver, especially C-reactive protein (CRP). A similar function is performed by other cytokines such as the leukemia inhibitory factor, oncostatin M, IL-1 and TNF. In-

terleukin-6 plays a role in iron and copper ions transport by regulation of transferrin, ceruloplasmin and haptoglobin concentrations [5]. A pyrogenic cytokine, IL-6 along with IL-1, TNF and INF can increase the body temperature by inducing the synthesis of prostaglandins. In addition, IL-6 activates the synthesis of glucocorticoids by secreting corticotropin and adrenocorticotropin [5]. Moreover, available data confirmed the IL-6 function in the inflammation, infections and trauma. Interleukin-6 activates the proliferation of mesangium in mesangioproliferative glomerulonephritis [5]. Elevated IL-6 levels were observed in patients with rheumatoid arthritis and were associated with the disease progression. Increased IL-6 levels were also documented in patients with Crohn disease and Castleman disease [12]. Scheller et al. [8] showed a role of the soluble receptor IL-6 – sIL-6R in chronic inflammation such as peritonitis, colitis, rheumatoid arthritis. The monoclonal antibodies to IL-6 or IL-6R therapy can be used in the treatment of inflammatory and autoimmune diseases [13].

Serum IL-6 concentrations rise in severe burns, sepsis and connective tissue diseases. It was suggested that IL-6 can be a factor reflecting the grade and extent of burns and the wound healing phase [14]. Concentration of this cytokine correlated with the extent of necrosis and concentration of acute-phase proteins. This indicated that IL-6 can be a useful diagnostic

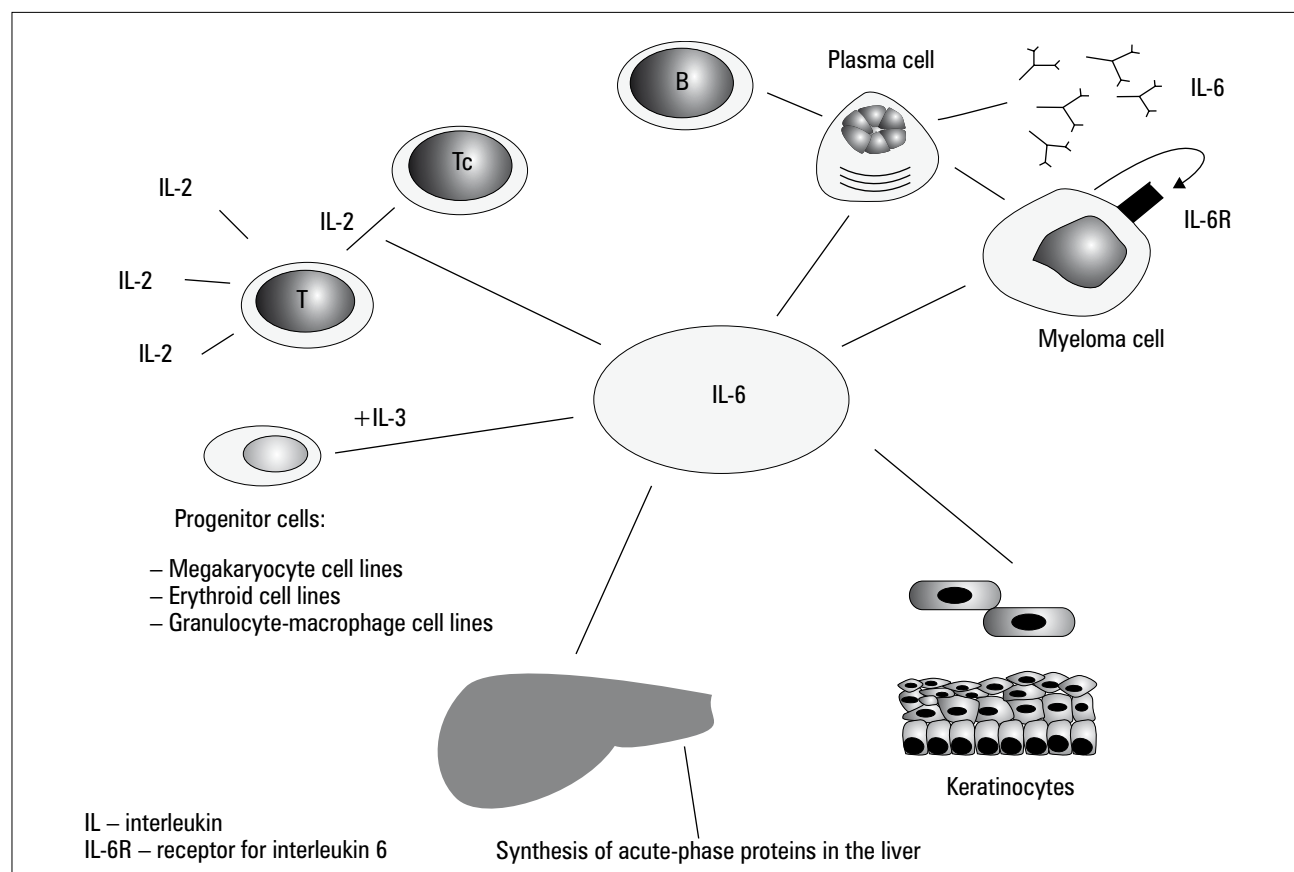


Fig. The biological activity of IL-6. Figure was prepared by authors based on [6].

Table. Clinical significance of interleukin-6 (IL-6)

Cancer type or related disorder	Characteristic IL-6	Use IL-6
Cancer type: Breast Colon Pancreatic Stomach	– increase in IL-6 serum levels associated with advanced stage, malignancy, tumor size, shorter survival in patients with this cancer – inhibition of apoptosis of cancer cells, induction of angiogenesis in tumor site	– negative prognostic factor – therapy with monoclonal antibodies to IL-6
Lymphoproliferative diseases: Multiple myeloma Leukemia Lymphoma	– autocrine and paracrine growth factor for multiple myeloma – increase in IL-6 serum levels associated with disease progression	– negative prognostic factor – therapy with monoclonal antibodies to IL-6 and IL-6R
Infectious and autoimmune diseases: Rheumatoid arthritis Crohn disease Castleman disease	– elevated serum concentration of IL-6 in acute phase, inducing the synthesis of acute-phase proteins, pyrogenic function	– marker for inflammation – therapy with monoclonal antibodies to IL-6R blocking IL-6
Burn	– elevated serum concentration of IL-6 associated with extent of burn and concentration of acute-phase proteins	– factor reflected grade and extent of necrosis and phase of wound healing
Bacterial infections, sepsis, acute pancreatitis	– elevated serum concentration of IL-6 in acute phase, pyrogenic and proinflammatory activity	– useful marker for diagnostics of bacterial infection and sepsis – prognostic factor in the early stage acute pancreatitis

IL-6R – interleukin-6 receptor

marker for bacterial infections and sepsis [15]. This cytokine may help in monitoring patients with acute pancreatitis. Chen et al. [16] showed that concentration of IL-6 is a prognostic factor in the early stage of acute pancreatitis. Moreover, Pihusch et al. [17] reported increased serum IL-6 concentrations in patients after transplantation, especially with inflammatory complications.

It has been reported that IL-6 plays a role in the pathogenesis of acquired immune deficiency syndrome (AIDS) by the chronic polyclonal B cell activation and the influence on hypergammaglobulinemia in AIDS [5]. Interleukin-6, TNF- α and IL-1 activate the replication of virus causes of AIDS (human immunodeficiency virus – HIV) [6]. The elevated concentration of IL-6 and overexpression of mRNA for this cytokine as well as the increased CRP concentrations were observed in HIV-positive patients [18]. Interleukin-6 is one of the growth factors for Kaposi sarcoma cells, the cancer often occurring in these patients [5].

Interleukin-6 as a prognostic factor

Interleukin-6 plays a major role in pathogenesis and development of malignancies. It helps tumor to grow through inhibiting cancer cells apoptosis and the induction of tumor angiogenesis [4]. IL-6 may be involved in the regulation of solid tumor growth in paracrine and autocrine ways [4]. Interleukin-6 contributes to the proliferation of colorectal cancer cells and other cancers, especially those at the advanced stage of devel-

opment [19]. Interleukin-6 concentrations can depend on the tumor stage and can correlate with survival.

Current investigations have focused on the use of IL-6 as a prognostic factor for cancer. Serum IL-6 concentrations are most commonly elevated in patients with endometrial cancer [20], lung cancer [21], colorectal cancer [22], renal cell carcinoma [23], breast cancer [4] and ovarian carcinoma [24]. Overexpression of IL-6 and its receptors (sIL-6R) was found in breast carcinoma [25] and in prostate cancer [3], where the concentration of this interleukin and its receptors correlated with the histological grade.

The findings of recent investigations confirmed the role of IL-6 in colorectal cancer. Serum concentration of IL-6 in patients with this cancer was associated with the disease progression, histological grade and bowel wall invasion [26]. Belluco et al. showed not only elevated serum IL-6 concentrations in patients with this cancer, but also the association between its levels and CEA as well as the disease progression. Moreover, this study demonstrated that serum IL-6 concentrations exceeding 10 pg/ml can be a negative, independent prognostic factor for colorectal cancer. Nikiteas et al. [27] reported that the serum concentrations of IL-6, CRP and TNF- α were elevated in patients with colorectal cancer compared with the control group. Serum concentrations of these cytokines correlated with the tumor size and were associated with shorter survival. The role of IL-6 as a prognostic factor was also confirmed by other authors [28]. Esfandi et al. [28] demonstrated that the colorectal cancer stage correlated not only with serum IL-6 concentrations, but also with the presence of IL-6 in colorectal cancer cells.

Zhang et al. [29] reported the autocrine production of IL-6 by breast carcinoma cells in conditions in vitro and in vivo. Significantly higher concentrations of IL-6 were documented in patients with breast carcinoma in the advanced tumor stage, especially with liver metastases. In patients with high IL-6 concentrations the response to treatment with chemotherapy and hormonotherapy was worse. These data indicate that serum IL-6 is an independent prognostic factor in patients with breast carcinoma, especially with progressive metastases. High IL-6 levels were associated with shorter survival in comparison with patients with its low concentrations. Moreover, the authors demonstrated a correlation between concentration of IL-6 and CRP in patients with breast carcinoma, which was also observed in other cancers, like colon cancer [27]. The results of a study by Salgad et al. [4] demonstrated a role of IL-6 as a prognostic factor in breast carcinoma. Moreover, Garcia-Tunon et al. [25] reported that the increased expression of IL-6 and its receptor is associated with the proliferative status of breast carcinoma cells and overexpression of bcl-2 gen.

Wallner et al. [30] suggested that for diagnostics of stomach cancer, serum IL-6 measurements might be used. They reported the significant association between concentration of IL-6 and the cancer stage. Elevated concentration of this cytokine was associated with the disease progression and its greater malignancy and thus IL-6 was a negative prognostic factor. The clinical role of IL-6 in the development of stomach cancer was documented by Ashizawa et al. (Tab.) [31]. The results indicated that IL-6 contributes not only to the development of stomach cancer, but also to the invasion of cancer cells to local lymph nodes and metastases, and these results confirmed the role of IL-6 as a prognostic factor. Huand et al. [10] showed a role of IL-6 in the induction of the VEGF production and, indirectly, in the stimulation of angiogenesis, which leads to tumor progression. The studies of Wu et al. [32] suggested that IL-6 could be a useful tool for monitoring the treatment and remission of stomach cancer. Concentrations of this cytokine correlated with the disease stage and increased in patients with recurrent stomach cancer [32].

The function of IL-6 in the pathogenesis and development of pancreatic cancer was documented by Bartsch et al. [33]. A study by Okada et al. [34] showed an association between serum IL-6 concentrations and the pancreatic cancer stage in patients with cachexia. Treatment with monoclonal antibodies to IL-6 can lead to a decrease of clinical symptoms in patients with high serum concentrations of this cytokine. Interleukin-6 can be released also by pancreatic cancer cells through paracrine or autocrine mechanisms [35].

The role of IL-6 in the pathogenesis of leukemia and lymphoma is well known. This glycoprotein is a β -cell stimulatory factor and mediates β -cell differentiation and the growth of β -cell lymphoid malignancies. El-Far et al. [36] reported elevated serum concentrations of this cytokine in patients with lymphoma and confirmed the role of IL-6 as an independent, negative prognostic factor. The authors suggested that IL-6 may be a prognostic marker also in patients with Hodgkin disease or

B-CLL [37]. Interleukin-6 plays a major role in the pathogenesis of multiple myeloma. Interleukin-6 is a growth factor for plasma cells and hybridoma cells derived from β -cell. Elevated IL-6 concentrations observed by Guo et al. [38] in patients with this cancer increased further in the disease progression. Recent studies have shown that IL-6 could be a target in the treatment of multiple myeloma by using monoclonal antibodies to IL-6 and IL-6R [39].

Pyrogenic activity of this proinflammatory cytokine makes it responsible for kachexia and the presence of fever, weight loss and other symptoms of the progressive disease. Dimitriu et al. [40] reported that cachexia is responsible for more than 20% of premature deaths in cancer patients. These data suggest that therapy based on monoclonal antibodies to IL-6 could improve survival of such patients and be used as a new strategy in the treatment of cancer patients with cachexia.

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