

REVIEW

Relationship between inflammation and cancer progression: review of the recent advances in interleukin-6 signaling and its blockage in cancer therapy

Takaya Nagasaki, Masayasu Hara, Kazuyoshi Shiga, Hiromitsu Takeyama

Department of Gastroenterological Surgery, Nagoya City University, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

Correspondence: Masayasu Hara

E-mail: mshara@med.nagoya-cu.ac.jp

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Interleukin-6 is a well-known pro-inflammatory cytokine with pleiotropic bioactivity and is mainly produced by inflammatory cells. Several diseases are influenced by interleukin-6; thus, the anti-interleukin-6 receptor antibody has been used clinically e.g., in the treatment of rheumatoid disease and Castleman disease. Signal transduction through gp130 occurs primarily via the Janus kinase (JAK)/signal transducer and activator transcription factor (STAT) pathway and secondarily via the phosphoinositide-3-kinase and mitogen-activated protein kinase pathways. Activation of STAT3 is an important step for the expression of various genes associated with carcinogenesis and cancer progression. Experiments using a STAT3 inhibitor and interleukin-6 shRNA have shown that the activation of STAT3 is necessary for cancer cell proliferation and survival. Several studies have also demonstrated that interleukin-6 exhibits characteristics associated with both inflammatory cytokines and proangiogenic factors. These studies have demonstrated that interleukin-6 contributes to angiogenesis as a potent inducer of vascular endothelial growth factor, which is one of the most important angiogenic factors. Recently, it has also been reported that cancer-stromal interactions are necessary steps during cancer progression, such as during angiogenesis. These various functions of interleukin-6, which affects cancer cells directly and through cancer-stromal interactions, are essential for cancer progression. Therefore, increasing attention is being paid to interleukin-6 signaling as a novel cancer therapeutic approach. This review summarizes the role of interleukin-6 signaling from the viewpoint of cancer progression and the potency of the anti-interleukin-6 signaling antibody during cancer therapy.

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Introduction

Since Rudolph Virchow first advocated a relationship between inflammation and cancer more than 150 years

ago, it has been recognized that inflammation resulting from either chronic disease or infection is an important risk factor in cancer progression ^[1]. Although a variety of cytokines are involved in inflammation, the cytokine

interleukin (IL)-6 has attracted recent attention due to its close relationship with cancer progression [2-4].

IL-6 is a multifunctional cytokine that binds to the IL-6 receptor to facilitate signal transmission. IL-6 is produced by various cells, including monocytes, macrophages, fibroblasts, and several types of tumor cells, where it plays a central role in the regulation of inflammatory and immune responses [5-7]. Several studies have indicated that IL-6 plays important roles in carcinogenesis and cancer progression related to proliferation, migration, and angiogenesis [8, 9], and its presence is associated with poor prognoses in several types of cancers [10-12]. Recently, IL-6 signaling has been investigated as a potential target for several types of cancer therapies [13, 14].

Conversely, the concept of “cancer-stroma interaction” (CSI) has been studied extensively [15-17]. Tumors consist of both cancer and stromal cells; for example, as much as 60-90% of the mass of colon cancers comprises stromal cells [18]. Recent studies have shown that cancer stromal cells contribute to various aspects of cancer progression, including migration, metastasis, and angiogenesis, involving the exchange of several cytokines during CSIs, and IL-6 appears to play an important role in CSI [19, 20]. Tumors exhibiting higher proportions of cancer stromal cells are of increasing interest as potential targets for alternative cancer therapies [21].

Since IL-6 signaling has already been extensively reviewed [2-9], the purpose of this review is to summarize the role of IL-6 signaling from the viewpoint of CSI, as well as the potency of IL-6 signaling in cancer therapy.

Interleukin-6 signaling

IL-6 is a pleiotropic cytokine that displays a broad spectrum of biological activities associated with immune regulation, hematopoiesis, inflammation, and oncogenesis. It was originally cloned in 1986 as the B-cell differentiation factor [22]. IL-6 is produced by various cells, including macrophages, T-cells, B-cells, fibroblasts, and several tumor cells, during acute and chronic inflammation [2, 4, 6]. IL-6 production is directly stimulated by prostaglandin E2 (PGE2) and transforming growth factor-beta (TGF- β), while IL-1 β and lipopolysaccharides indirectly stimulate IL-6 production via nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation [23-25].

For target cells, IL-6 first binds to the IL-6 receptor (IL-6R). The complex of IL-6 and IL-6R then associates with the signal transducing protein gp130, inducing its dimerization and initiating signaling.

IL-6 signaling is transmitted via IL-6R and is characteristic of the existence of soluble IL-6R. During IL-

6 signaling, IL-6R adopts two forms: membrane-bound IL-6R (mIL-6R) and a soluble form (sIL-6R). Signaling through mIL-6R and sIL-6R has been categorized as “classic signaling” and “trans-signaling,” respectively (Fig1). Of these, trans-signaling represents the main pathway, because mIL-6R is expressed on restricted cells such as hepatocytes and some leukocytes, while sIL-6R occurs naturally in body fluids, and gp130 is widely expressed on most cells [26]. Although only limited information is currently available regarding sIL-6R, it is believed that sIL-6R is generated by shedding of mIL-6R, and is supplied abundantly through body fluid [27]. Signal transduction through gp130 occurs primarily via the Janus kinase (JAK)/signal transducer and activator transcription factor (STAT) pathway and secondarily via the phosphoinositide-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways [28]. While IL-6 signaling is essential for biological activity, overexpression of IL-6 leads to physical disorders, and therefore, negative regulation of IL-6 signaling is mediated by the suppressor of cytokine signals (SOCS) pathway [22].

The presence of the soluble form of gp130 (sGP130) is another characteristic of IL-6 signaling. As with sIL-6R, sGP130 also exists abundantly in body fluids, where it combines with the IL-6 and IL-6/sIL-6R complex, thereby inhibiting coupling with membrane-bound GP130 as a natural antagonist of IL-6 signaling [26].

IL-6 signaling in cancer progression

The relationship between chronic inflammation and cancer progression or carcinogenesis has been widely recognized, as observed with inflammatory bowel disease in colon cancer or *Helicobacter pylori* infection in gastric cancer. Numerous studies have demonstrated that various forms of inflammation-associated cytokines, including IL-6, are associated with carcinogenesis or cancer progression [29-31].

Activation of STAT3, located downstream of IL-6, has been shown to be an important step for promotion and progression of various genes associated with carcinogenesis and cancer progression, including proliferation, angiogenesis, invasion, and metastasis [32-35]. Becker *et al.* reported that in colitis-associated cancer in AOM+DSS mouse models, IL-6 stimulation contributed to the development of intestinal tumors, which was subsequently suppressed by the IL-6 receptor antibody [36]. Similarly, in another study, using STAT3 inhibitor and IL-6 shRNA, Lin *et al.* revealed that activation of STAT3 is necessary for colon cancer cell proliferation and survival [32].

In clinical evaluations of several cancer types, serum IL-6 concentrations are often elevated in patients with

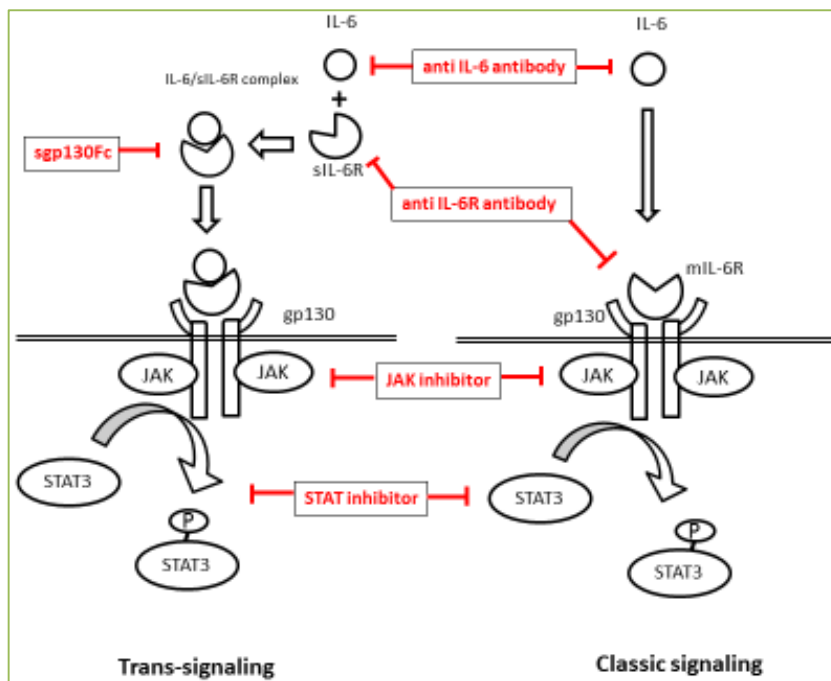


Figure 1. Trans-signaling. The IL-6 and sIL-6R complex interacts with gp130 on target cells and induces activation of JAKs and phosphorylation of STAT3. **Classic signaling.** IL-6 interacts with mIL-6R on target cells and activates the JAK/STAT pathway.

cancer, and these concentrations correlate with their prognoses or responses to cancer therapy. One such study indicated that the preoperative serum IL-6 level is a relevant biomarker of long-term cancer progression and in patients with colon cancer [11], the preoperative serum IL-6 levels correlated with tumor size, lymph node metastasis, distant metastasis, and survival time [10]. Studies have also reported that serum IL-6 levels correlated with prognoses of ovarian cancers [14], or that serum sIL-6R, in addition to IL-6, correlated with prognoses of colorectal cancer [10]. Neither of these studies reported that preoperative serum IL-6 levels correlated with tumor size, lymph node metastasis, or distant metastasis, although a correlation was observed between serum sIL-6R and lymph node metastasis and survival.

In addition to its role as a biomarker for survival time, IL-6 may also function as a biomarker to predict the results of chemotherapy. For example, a recent study reported that serum IL-6 and IL-1 β can predict the efficacy of gemcitabine for treatment of pancreatic cancer [12].

Finally, while IL-6 per se has not been recognized as an effective biomarker for cancer prognosis, research suggests that it may serve as a predictive biomarker [37].

IL-6 signaling in cancer-stromal interaction

Recent studies have revealed that not only cancer cells

but also stromal cells play important roles in IL-6 signaling. Extensive studies on the concept of CSI have demonstrated that stromal cells are indeed important for cancer progression. Tumors consist of both cancer cells and stromal cells, and the stromal cells are composed of fibroblasts, inflammatory cells, pericytes, and smooth muscle cells. In fact, the main cellular constituents of solid tumors are stromal fibroblasts [20].

In recent years, cancer stromal fibroblasts have been investigated as a central player of CSI. Cancer stromal fibroblasts differ from normal fibroblasts and have specific effects on tumor growth; thus, they are often referred to as cancer-associated fibroblasts (CAFs) [38, 39]. CAFs are activated fibroblasts observed in cancer stroma. For example, in breast cancer, approximately 80% of stromal fibroblasts reportedly acquire this activated phenotype [19]. These are commonly identified by their properties as myofibroblasts and differ from normal fibroblasts in that they express alpha-smooth muscle actin [40]. However, their origins are not yet fully understood, and different theories explain them as a result of epithelial-mesenchymal transition (EMT) from cancer cells [19] or as cells recruited from bone marrow [41]. Other theories have suggested that cancer cell stimulation converts normal fibroblasts to activated cancer stromal fibroblasts. The results of our research have indicated that both cancer stromal fibroblasts and benign fibroblasts can be

stimulated to an activated phenotype by cancer cells [42].

Several studies have also demonstrated that CAFs play a critical role in cancer progression through the production of several cytokines, growth factors, and angiogenesis factors, thus leading to cancer proliferation, migration, angiogenesis, and metastasis [43, 44].

IL-6 signaling plays an important role in CSI, and studies have indicated that cancer cells are both the main producer and receiver of IL-6 in IL-6 signaling associated with malignant tumors. In addition to the important role of cancer cells in IL-6 signaling, cancer stromal fibroblasts have recently begun to attract attention as having a major role in IL-6 signaling with a focus on gastrointestinal cancer.

The results of our studies have revealed that cancer-stromal fibroblasts play an important role as a producer of IL-6 in colon CSI. Immunohistochemical staining revealed that in colon cancer, IL-6 expression was predominantly localized in the stromal compartment rather than the cancer cells. Stromal fibroblasts isolated from colon cancer produced more IL-6 than cancer cells. Evidence also suggests that cancer cells may cause fibroblasts to initiate an inflammatory response, thus promoting IL-6 expression. Fibroblasts from the non-cancer section separately co-cultured with cancer cells strongly induced IL-6 expression, which may be due to inflammatory cytokines such as IL-1 β and tumor necrosis factor alpha (TNF- α) [42]. Similarly, research has suggested that gastric cancer stromal fibroblasts stimulated by cancer cells are the main producers of IL-6 in gastric CSI [45].

IL-6 signaling in cancer angiogenesis

The progressive growth of malignant tumors is dependent on angiogenesis, which is regulated by proangiogenic and antiangiogenic molecules. The proangiogenic regulators induce vascular endothelial cells to form tube structures, which bring nutrition and oxygen to the developing tumor. Angiogenesis is one of most representative contributions of CSIs related to cancer progression.

Recent studies have demonstrated that IL-6 exhibits aspects associated with both inflammatory cytokines and with proangiogenic factors. Some studies have suggested that IL-6 contributes to angiogenesis as a potent inducer of vascular endothelial growth factor (VEGF), which is one of the most important angiogenic factors. Wei *et al.* reported that IL-6 induced VEGF production in C33A cervix cancer cells, which was then suppressed by the inhibition of IL-6 signaling in vitro and in vivo [35]. As previously noted, both cancer cells and stromal cells play important roles in cancer angiogenesis. Our group has

demonstrated that IL-6 stimulation induces colon stromal fibroblasts to produce VEGF and vascular tube formation in an in vitro angiogenesis model [42]. Furthermore, in animal experiments, we have demonstrated that VEGF expression and vasculogenesis in xenografted cancers are suppressed by inhibition of host stromal IL-6 signaling using anti-IL-6 receptor antibody [42] (Fig2).

Although it is well known that IL-6 acts as a proangiogenic cytokine, the mechanism by which IL-6 induces angiogenesis is not fully understood. Several potential IL-6-related angiogenesis pathways have been hypothesized. Anglesio *et al.* reported that IL-6 signaling via STAT3 induced HIF expression, leading to angiogenesis in ovarian cancer [13], while Niu *et al.* reported that STAT3 activity stimulated VEGF expression through the VEGF gene promoter, and that blocking STAT3 in tumor cells down regulated VEGF expression [33].

Conversely, other studies have reported that macrophages that infiltrate tumor stroma, also known as tumor-associated macrophages (TAMs), play important roles in cancer angiogenesis. For example, Duluc *et al.* reported that IL-6 skews monocyte differentiation into TAM characteristics. TAMs are known to induce angiogenesis through secretion of proangiogenic factors such as VEGF, TGF- β , fibroblast growth factor (FGF), and IL-8 [46].

Although direct consequences with IL-6 were not mentioned, Shao *et al.* reported that PGE2 induced myofibroblasts to produce VEGF and other angiogenesis-related growth factors such as hepatocyte growth factor, which led to angiogenesis [47]. PGE2 was apparently generated by IL-6 stimulation through cyclooxygenase2 in various cells; therefore, the IL-6-PGE2-VEGF cascade may play an important role in cancer angiogenesis. However, given the limited availability of data, further studies are required to clarify the mechanism through which IL-6 induces cancer angiogenesis.

IL-6 signaling as a therapeutic target

As noted above, IL-6 signaling and the subsequent associated STAT3 activation have been shown to correlate with cancer progression and poor prognosis. Consequently, IL-6 signaling is considered a novel potential therapeutic target for treatment of various cancers. Methods have been developed to inhibit the IL-6/STAT3 pathway for the treatment of IL-6-associated diseases such as rheumatoid arthritis and Castleman disease, but not for cancers. Different efforts focused on the inhibition of IL-6 signaling have included the use of anti-IL-6 antibodies, anti-IL-6R antibodies, soluble gp130, and some selective small molecules representing

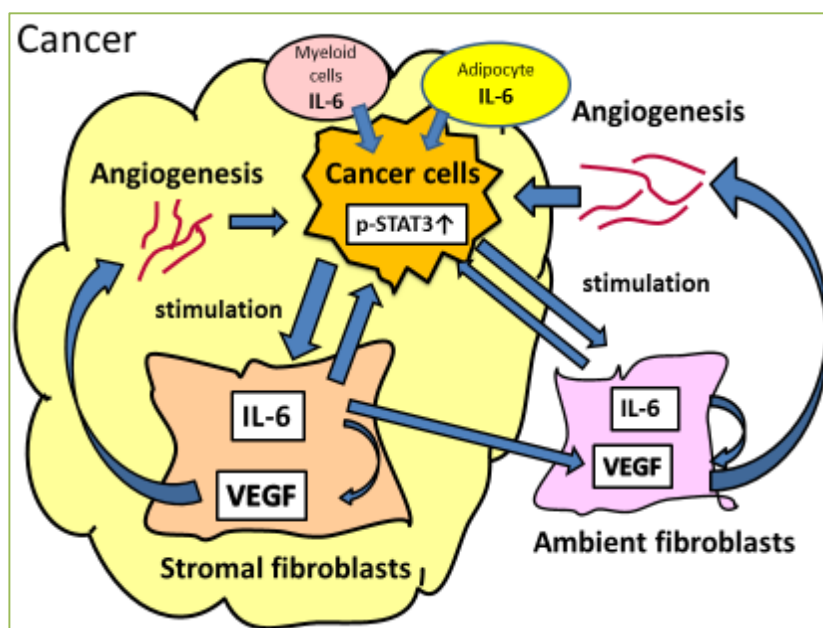


Figure 2. Angiogenesis through IL-6 signaling in cancer stromal interaction. Stromal fibroblasts stimulated by cancer cells produce IL-6. IL-6 induces fibroblasts to produce angiogenic factors such as VEGF in an autocrine/paracrine manner.

JAK/STAT inhibitors (Fig.1).

Anti-IL-6 antibodies

Anti-IL-6 antibodies include the chimeric murine-human monoclonal antibody siltuximab, and the fully human monoclonal antibody sirukumab. Anti-IL-6 antibodies were the first therapeutics designed to target IL-6 signaling in clinical studies on human cancers during the 1990s, including multiple myeloma and acquired immunodeficiency syndrome (AIDS)-associated Kaposi's sarcoma, using murine antibodies. However, these treatments produced only limited responses before onset of the immune response [48]. This led to subsequent development of chimeric murine-human monoclonal anti-IL-6 antibody siltuximab.

Although few studies have reported the use of siltuximab to treat colon cancer, other studies have reported the use of siltuximab to treat other types of malignancies, such as ovarian cancer, prostate cancer, renal cancer, and multiple myeloma [14, 49-51]. Coward *et al.* reported that siltuximab inhibited ovarian cancer cell lines from releasing several cytokines, including IL-6 [14]. That study also reported that siltuximab inhibited *in vivo* angiogenesis and tumor growth in xenografted ovarian cancer tumors. More recently, a clinical study analyzing the effect of siltuximab in various solid cancers, including colorectal cancer, was conducted, although the results have yet to be published. *Anti-IL-6R antibodies*

One of the anti-IL-6R antibodies previously evaluated was the humanized anti-IL-6R monoclonal antibody to cilizumab, which blocks both soluble IL-6R and membrane-bound IL-6R. Tocilizumab is currently used clinically to treat IL-6-dependent chronic inflammatory disease. While this has not been used clinically for cancer therapy, several preclinical studies have been reported. As noted above, research completed in our laboratory reported the anti-cancer effects of tocilizumab with a colon cancer xenograft model [42]. The results of that research indicated that tocilizumab affects stromal cells by promoting anti-angiogenic activity, rather than by directly inhibiting cancer cells. Similarly, another study reported that tocilizumab with interferon inhibited the growth of renal cell carcinoma, both *in vitro* and *in vivo*, through suppressed SOCS3 expression [52]. Although few studies involving the use of tocilizumab for colon cancer therapy have been reported to date, additional studies are expected in the near future.

sgp130Fc

Another approach to specifically inhibit IL-6 trans-signaling involved using a modified soluble form of gp130, which acts as an antagonist of the IL-6/sIL-6R complex. This protein construct, Sgp130Fc, combined the extracellular component of gp130 with the Fc portion of the human IgG1 antibody. Sgp130Fc is currently being evaluated in preclinical experimental models of cancer, as well as for other diseases, and preliminary research

suggests that it may be effective as treatment for colorectal cancer [2].

JAK/STAT inhibitors

JAK/STAT inhibitors have also been investigated as potential IL-6 signaling inhibitors in preclinical experimental models, and the small molecule JAK2 inhibitor CEP-33779 reportedly reduced tumor growth in experimental models of colitis-associated colon cancer [21, 53].

Conclusions

It is clear that IL-6 is an important tumor-promoting cytokine that induces cell proliferation, angiogenesis, and migration in various cancers, including colorectal cancer. IL-6 signaling appears to occur within the cancer cells, and during CSIs, thus making it a potentially effective therapeutic target.

Data from both experimental models and clinical studies strongly suggest that targeting IL-6 signaling may improve the prognosis of various cancers, including colorectal cancer, and that improved therapy may be achieved by combining anti-IL-6 therapy with conventional cancer therapies that directly affect cancer cells. The efficacy of this approach, however, will require additional studies and further clinical trials.

Conflicting interests

The authors declare that they have no conflicting interests.

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