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Interleukin-6 signaling pathway in targeted therapy for cancer

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SUMMARY

Interleukin-6 (IL-6) is a multifunctional cytokine which plays an important role in a wide range of biologic activities in different types of cell including tumor cells. IL-6 is involved in the host immune defense mechanism as well as the modulation of growth and differentiation in various malignancies. These effects are mediated by several signaling pathways, in particular the signal transducer and transcription activator 3 (Stat3). There exists abundant evidence demonstrating that deregulated overexpression of IL-6 was associated with tumor progression through inhibition of cancer cell apoptosis, stimulation of angiogenesis, and drug resistance. Clinical studies have revealed that increased serum IL-6 concentrations in patients are associated with advanced tumor stages of various cancers (e.g., multiple myeloma, non-small cell lung carcinoma, colorectal cancer, renal cell carcinoma, prostate cancer, breast cancer and ovarian cancer) and short survival in patients. Therefore, blocking IL-6 signaling is a potential therapeutic strategy for cancer (i.e., anti-IL-6 therapy) characterized by pathological IL-6 overproduction. Preliminary clinical evidence has shown that antibody targeted IL-6 therapy was well tolerated in cancer patients. In this review, we detail the progress of the current understanding of IL-6 signaling pathway in cancer as well as an antibody targeted IL-6 therapy for human cancer.

Introduction

Initially identified as a T-cell-derived regulating factor in B cell differentiation, Interleukin-6 (IL-6, a glycoprotein composed of 184 amino acids and of 26 kDa in molecular weight) is now known as a multi-functional cytokine.[1–5] Following the cloning of IL-6 DNA, it has been shown that IL-6 can be produced by various cell types, including tumor cells. IL-6 plays important roles in with a wide range of biological activities in immune regulation, hematopoiesis, and oncogenesis. IL-6 has been found to be involved in normal cell inflammatory processes, host immune defense mechanisms, and modulation of cellular growth. IL-6 is able to cross the blood–brain barrier and resulting synthesis of PGE2 in the hypothalamus, thereby changing the body's temperature set point.[6] In normal muscle tissue, IL-6 stimulates energy mobilization which leads to increased body temperature. IL-6 can be secreted by macrophages in response to specific microbial molecules. IL-6 stimulates acute phase protein synthesis, and increases the production of neutrophils in the bone marrow. It promotes the growth of B cells and is antagonistic to regulatory T cells. Most importantly, IL-6 is involved in the proliferation and differentiation of various malignant tumor cells.[7,8] For example, increased production of IL-6 has been implicated in a wide range of cancers, such as multiple myeloma (MM),[9–11] endometrial cancer,[12] lung cancer,[13] colorectal cancer,[14] renal cell carcinoma,[15,16] cervical cancer,[17] breast cancer[18,19] and ovarian carcinoma.[20,21] Overexpression of both IL-6 and its receptors (IL-6R and sIL-6R) has been found in breast carcinoma,[18] prostate cancer[22] and oral squamous cell carcinoma (OSCC).[23] Elevated levels of IL-6 have been found in culture supernatant of multidrug resistant cell lines[24–27] and the elevated IL-6 levels in the serum of cancer patient have been associated with poor clinical outcomes.[28–30] These findings suggest that blocking IL-6 may prove to be therapeutic for cancer in which IL-6 is overproduced.

Targeted chemotherapy is an area of great potential in cancer therapy. Targeted anti-IL-6 antibody therapy has been used in clinical trials and found to be well tolerated in patients of different cancers, including ovarian cancer, breast cancer, multiple myeloma, renal cell carcinoma, and B-lympho-proliferative disorders.[28,31] Recent studies show that CNTO 328, a chimeric murine anti-human IL-6 antibody, can neutralize the function of IL-6 and reduce the incidence of cancer-related anorexia and cachexia without serious adverse effects.[28,31]

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In the present review, we describe the advance in IL-6 signaling pathway and detail the progress of the current state-of-the-art methods to treat cancers by targeting the IL-6 antibody. We first present the biology of IL-6 and discuss IL-6 as a prognostic factor for cancer. Then, we summarize recent advances in the antibody targeted IL-6 therapy for cancer. Last, we discuss the current challenges and future prospects of targeting IL-6.

IL-6 signaling pathway in cancer

IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding protein of IL-6Rα chain (also called CD126), and the signal-transducing component gp130 (also called CD130). IL-6 belongs to a cytokine family comprising IL-6, IL-11, leukaemia inhibitory factor (LIF), oncostatin M (OSM), ciliar neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophinlike cytokine (CLC).[32,33] These cytokines share a common glycoprotein 130 receptor (gp130) component[34] that modulates the transcription of several liver-specific genes during acute inflammatory states. IL-6 affects cell behavior through receptor type I, which is a type of hematopoietic cytokine gp130 receptor expressed in lymphoid and nonlymphoid cells as well as malignant cells. There are two types of receptor for IL-6, i.e., cell membrane IL-6 receptor (IL-6R) with low affinity that forms a complex with gp130 after binding with IL-6 and activating the tyrosine kinase JAK, and a soluble IL-6 receptor (sIL-6R) which binds with IL-6 and then with the membrane receptor β chain – gp130, leading to the intracellular signal.[35,36]

The signal transduction of IL-6 involves the activation of janus kinase (JAK) tyrosine kinase family members, resulting in the activation of transcription factors of the signal transducers and activators of transcription 3 (Stat3).[32,36] (Fig. 1). A variety of events take place downstream of gp130 activation through the ligand, including the activation of cytoplasmic tyrosine kinases and the modification of transcription factors. Although gp130 has no intrinsic kinase domain, the JAK1, JAK2 and tyrosine kinase2 (TYK2) of the JAK family are found to be associated constitutively with gp130 and are activated in response to IL-6 family members.[32,33,37] The activation of these kinases, in turn, leads to tyrosine phosphorylation of the Stat3. Following phosphorylation and acetylation, Stat3 forms a dimer in which the SH2 domain of one phospho-Stat3 (pStat3) molecule binds to the phosphorylated Tyr^{705} of the other and vice versa. The pStat3 dimer then translocates from the cytoplasm to the nucleus.[38] Within the nucleus, pStat3 dimers recognize and bind a canonical 8–10 base pair inverted repeat DNA element with a consensus sequence 5′-$TT(N_{4-6})AA$-3′ that is commonly referred to as an interferon (IFN)-gamma activated sequence (GAS) element. The engagement of pStat3 dimers then initiates a change in the transcription of a number of genes including the apoptotic regulatory genes $BcL\text{-}X_L$, MCL-1, XIAP, c-myc, and Fas.[39] The termination and modulation of the IL-6-Jak-Stat3 signalling pathway is mediated by the SOCS (suppressor of cytokine signalling) feedback inhibitors and PIAS (protein inhibitor of activated Stat) proteins (Fig. 1). Stat3 also binds to p53 and inhibit its function as a regulator of apoptosis. Although the full spectrum of pStat3 target genes is not well defined, Stat3 has been identified as the prime transcriptional regulator mediating the IL-6 dependent cell growth, differentiation, and survival signals.[33,40] This critical function of Stat3 is supported by experiments demonstrating that the transfection of dominant-negative Stat3 completely inhibits the anti-apoptotic effect of IL-6 in carcinoma cells.[41] In addition to Stat3 signaling pathway, IL-6 also activates Ras, MAPK, Cox-2, Wnt and PI3K/AKT pathways.[42,43] These different pathways together contribute to the pro-tumorigenic and antiapoptotic activities of IL-6. In myeloma cells, at least two independent pathways by which IL-6 can activate PI3K and AKT, One pathway was mediated through RAS activation which was independent of p85, and a second that was mediated via p85 and a Stat3-containing complex. Additional studies in oncogenic, mutated RAS-containing myeloma cells confirmed the existence of the RAS-mediated pathway of PI3K-AKT activation.[44] In another study, IL-6 was dependent on c-Met signaling in activating both Ras and p44/42 MAPK by a mechanism involving the tyrosine phosphatase Shp2.[45]

Potential roles of IL-6 in cancer

IL-6 is one of the most ubiquitously deregulated cytokines in cancer, with over-expression of IL-6 observed in virtually every tumor that has been studied.[12,46–48] Several investigators have

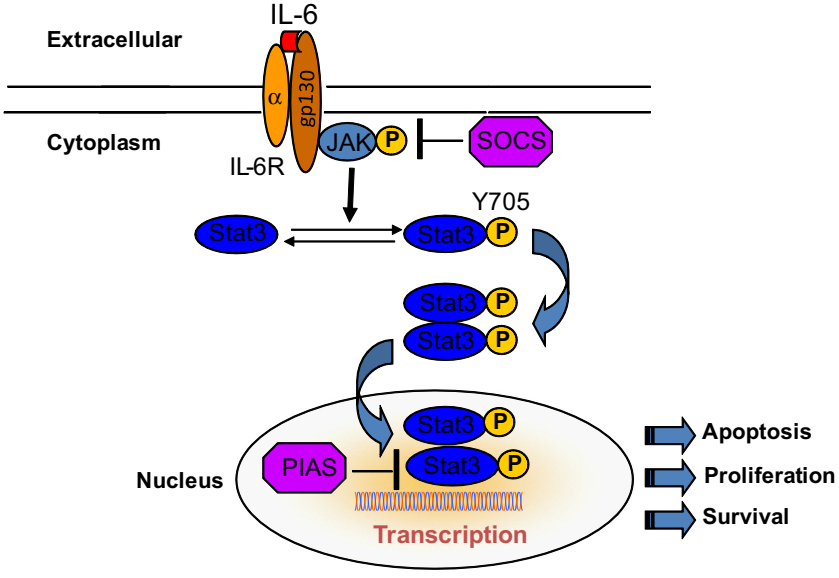

Fig. 1. IL-6-Jak-Stat signaling pathway. IL-6 binds to the IL-6R and induces a cascade of phosphorylation JAK kinase that leads to the activation of Stat3. Activated Stat3 translocates to the nucleus where it targets genes involved in apoptosis, proliferation and survival. SOCS and PIAS proteins negatively suppress IL-6-Jak-Stat pathway activity.

Table 1
Potential roles of IL-6 in tumorigenesis.

Cancer	Related factor (s)	Mechanism (s)	Refs.
Multiple myeloma	Myc, Stat3, FGFR	Transformation, growth	83,84
Ovarian cancer	Stat3, VEGF	Growth, drug resistance	70,71
Lung cancer	EGFR, Stat3	Transformation	72–74
Bladder cancer	NF-kappaB	Transformation	75–77
Breast cancer	Notch, Ras, HER2	Transformation	68,78,79
Colon cancer	Stat3, c-Myc	Proliferation	80
Prostate cancer	IGF-1R, ErbB2	Growth	81,82

reported an aberrant IL-6 pathway activation in a variety of human cancer cell lines and solid tumors, including epithelial tumors of ovary, breast and prostate as well as multiple myelomas, leukemias and lymphomas.[12,21,48–52] IL-6 has been found to play an important role in various tumor behaviors including the development, cell migration, invasion, growth of malignancies,[53] proliferation, apoptosis,[54] progression,[28,55] angiogenesis and differentiation of tumor cells.[56] For example, IL-6 aids tumor growth by inhibiting cancer cell apoptosis and inducting tumor angiogenesis,[57,58] and contributes to the proliferation of colorectal cancer cells and other cancers, especially at the advanced stage of development.[59] IL-6 has also been shown to enhance endothelial cell migration,[60] a key step in angiogenesis, and dissemination of solid tumors. Furthermore, certain tumors including myeloma, AIDS associated Kaposi sarcomas, and some T and B-cell lymphomas are all stimulated by IL-6.[29,61]

The role of IL-6 has been related to other factors. For example, IL-6 regulates tumor cell proliferation through activation epithelial growth factor, hepatocyte growth factor and other factors.[62–65] It stimulates angiogenesis and tumor vascularisation through regulates vascular endothelial growth factor (VEGF) synthesis.[66]

In cancer stem cell studies, IL-6 has been implicated as a potential regulator of normal and tumor stem cell self renewal.[67,68] Human primary mammospheres (MS) from node invasive breast carcinoma tissues expressed higher IL-6 levels than MS from matched non-neoplastic mammary glands did. IL-6 mRNA was detected only in basal-like breast carcinoma tissues, which is an aggressive breast carcinoma variant exhibiting stem cell features. IL-6 treatment triggered Notch-3-dependent upregulation of the Notch ligand Jagged-1 and promoted MS and MCF-7-derived spheroid growth. Moreover, IL-6 induced the Notch-3-dependent upregulation of the carbonic anhydrase IX gene and promoted a hypoxia-resistant/invasive phenotype in MCF-7 cells and MS. Finally, autocrine IL-6 signaling relied heavily upon Notch-3 activity to sustain the aggressive features of MCF-7-derived hypoxia-selected cells.[68] These studies support the hypothesis that IL-6 induces malignant features in Notch-3-expressing stem/progenitor cells from human ductal breast carcinoma and normal mammary glands. Recently, the IL-6 downstream protein Stat3 has been found to regulate cancer stem cells in brain tumors as well.[69] When Stat3 is inhibited, cancer stem cells in glioblastomas lose their stem-cell characteristics permanently, suggesting that Stat3 regulates the growth and self-renewal of stem cells within glioblastomas. Strikingly, a single, acute treatment with Stat3 inhibitors was effective, implying that a Stat3 inhibitor does in fact stop tumor formation.[69] In summary, the potential roles of IL-6-Jak-Stat signaling pathway in tumorigeneis have been reported in different tumor models, including ovarian,[70,71] lung,[72–74] bladder,[75–77] breast,[68,78,79] colon,[80] prostate cancer,[81,82] and multiple myeloma[83,84] (Table 1).

IL-6 has also been correlated with cancer drug resistance where modulating the IL-6 pathway directly affects the cellular resistance to drug treatments. For example, breast cancer cells that are sensitive to drug treatment do not express IL-6, but multi-drug resistant breast cancer cells produce high levels of IL-6.[51] IL-6 is found to be an autocrine and paracrine growth factor for prostate cancer cell lines and serves as a resistance factor for cisplatin-mediated cytotoxicity.[50] Treatment with combined cisplatin and an anti-IL-6 or IL-6R antibody reverses the cisplatin resistance of renal carcinoma cell lines *in vitro*.[85] Similarly, exogenous IL-6 treatment rendered tumor cells resistant to apoptosis induced by a number of cytotoxic agents including doxorubicin, VP-16 and cisplatin.[26] In contrast, specific blockade of IL-6 by antisense oligonucleotide sensitized the effect these drugs had on tumor cells.[26] Finally, we and others have shown that IL-6 production is increased in ovarian cancer cell lines resistant to paclitaxel as well as in serum and ascites of ovarian cancer patients.[21,24,46,49] Stat3 is overexpressed in most paclitaxel-resistant ovarian cancer cells. Inhibition of Stat3 activation results in significant decreases in paclitaxel resistance and enhanced apoptosis. Drug-resistant recurrent tumors have significantly greater phosphorylated Stat3 (pStat3) expression as compared with matched primary tumors. Tumors with associated inflammatory cell infiltrates also have a higher proportion of cells staining intensely for nuclear phosphorylated Stat3 as compared with tumors without inflammatory infiltrates, consistent with paracrine activation of the Stat3 pathway by immune-mediated cytokines IL-6.[86] IL-6 is also promoting tumor cell to escape cell death induced by chemotherapy drugs. IL-6 increases the expression of several antiapoptotic proteins through Stat3. Together, these data strongly support the theory that IL-6 is a potent and clinically important regulator of anti-apoptotic gene expression and drug resistance.

Preclinical and translational findings indicate that IL-6 plays an important role in diverse malignancies and provides a biologic rationale for targeted therapeutic investigations. The success in treating certain diseases with drugs that antagonize IL-6 signaling has since provided further support for a pathological role of IL-6 in cancer. Various compounds antagonize IL-6 production, including corticosteroids, nonsteroidal anti-inflammatory agents, estrogens, and cytokines.[87] However, as expected, these drugs also have effects on tumor cells that far beyond their anti-IL-6 properties.[28] Current targeted biological therapies mainly focus on IL-6-conjugated toxins and mAbs against IL-6 and IL-6R.[11,88] For example, the CNTO 328 antibody has been shown to be capable of neutralizing IL-6's function in different types of human cancer including multiple myeloma[89], ovarian cancer,[18,28,90–92] and prostate cancer.[93] Our study shows CNTO 328 specifically suppressed IL-6 induced Stat3 phosphorylation and Stat3 nuclear translocation. Treatment with CNTO 328 significantly decreased Stat3 downstream protein levels, including MCL-1, Bcl-X_L and survivin. CNTO 328 also increased the cytotoxic effects of paclitaxel in a paclitaxel resistant ovarian cancer cell line *in vitro* (unpublished data). The down-regulation of IL-6 signaling using the CNTO 328 can enhance the antitumor activity of the proteasome inhibitor bortezomib in multiple myeloma by attenuating inducible chemoresistance.[90] For example, treatment of both IL-6-dependent and IL-6-independent multiple myeloma cell lines with CNTO 328 enhanced the cytotoxicity of bortezomib. CNTO 328 enhanced bortezomib-mediated activation of caspase-8 and caspase-9, and attenuated bortezomib-mediated induction of antiapoptotic hsp-70.[89,90]

Methods based on humanized anti-IL-6R mAb (rhPM-1, IgG1class) have also been developed, such as PM1 tested in patients with MM and rheumatoid arthritis. Other methods include using a mixture of anti-IL-6 or anti-IL-6R mAbs that can shorten the half-life of the IL-6/IL-6R complexes (from 4 days to less than 20 min) *in vivo*.[94,95] Tocilizumab (namely MRA) is a humanized antihuman IL-6R antibody engineered by grafting the complementarily determining regions of a mouse anti-human IL-6R antibody into human IgG1κ to create a human antibody with a human IL-6R binding site.[95] Tocilizumab binds to the IL-6-binding site of

human IL-6R and inhibits IL-6 signaling, leading to the neutralization of IL-6 activities.[96]

More recently, a novel high-affinity fully human anti-IL-6 mAb, 1339 has been developed.[9] The mAb 1339 significantly inhibited the growth of multiple myeloma cells in the presence of bone marrow stromal cells *in vitro*. This is associated with the inhibition of phosphorylation of Stat3, extracellular signal-regulated kinase 1/2, and AKT. In addition, mAb 1339 enhanced the cytotoxicity induced by dexamethasone, and other drugs including bortezomib, lenalidomide, and perifosine in a synergistic fashion. More importantly, mAb 1339 significantly enhanced the growth inhibitory effects of dexamethasone *in vivo* in a SCID-hu mouse model of multiple myeloma. The mAb 1339 treatment also resulted in the inhibition of osteoclastogenesis *in vitro* and bone remodeling in SCID-hu mode. In addition, several small molecule compounds inhibit IL-6 or IL-6 downstream proteins have been developed and currently being evaluated in preclinical and clinical models of cancer.[42]

IL-6 as a prognostic factor for cancer

IL-6 concentrations have been found to depend upon tumor stage, which is correlated with patient survival. For example, serum IL-6 concentration in patients is associated with the progression, histological grade, bowel wall invasion,[97,98] as well as tumor size and shorter survival periods[99] of colorectal cancer. Serum IL-6 concentration has also been found to be correlated with the different stages of pancreatic cancer in patients with cachexia.[100] Higher serum and ascites levels of IL-6 have been found in patients with ovarian cancer, which have been shown to correlate with the extent of the disease and poor clinical outcome.[41,49,50,57,101] Existing studies report that the concentrations of IL-6 were significantly higher in patients with breast carcinoma in the advanced stage of the tumor, especially those having liver metastases.[102] In patients with high IL-6 concentrations, the response to treatment with chemotherapy and hormone therapy was worse.[102] Patients with higher IL-6 levels have a shorter survival while a reduction in the levels of IL-6 was visible in patients who responded better to therapy.[101,102] Our recent study in ovarian cancer shows there is a trend toward greater IL-6 expression in the recurrent tumors as compared with the matched primary tumors. There is also an increase in the intensity of IL-6 expression in the recurrent metastatic lesion as compared with the primary metastasis.[103] These results suggest that IL-6 has the potential to be used as an independent prognostic factor for cancer. For example, the role of IL-6 as a prognostic factor has been found in stomach cancer[104–106] and breast carcinomas.[19]

Targeting IL-6 with monoclonal antibody for cancer therapy

Most of the clinical experience in direct inhibition of IL-6 for cancer therapy has been with the use of murine or humanized monoclonal antibodies (McAbs). Several IL-6 antibodies have been developed in recent years and evaluated in clinical trials, such as anti-IL-6 chimeric McAb, CNTO 328 (Siltuximab) developed by Centocor and BE-8, developed by Diaclone.[9,28,31] Earlier investigations used BE-8, a murine anti-IL-6 monoclonal antibody which is, however, associated with several problems.[28] For example, BE-8 cannot efficiently block the daily production of IL-6 levels >8 mg.[28,107] Moreover, it is difficult to suppress delayed IL-6 production without performing repeated dosing due to the short half-life of BE-8 (3–4 days). This is a challenge as murine antibodies generally are neutralized by human antimouse responses.[28,108] On the other hand, CNTO 328 is a human-mouse chimeric antibody, constructed from a murine anti IL-6 McAb, with anti-tumor and anti-inflammatory activities.[31,108] It contains the antigen-binding region of the human immunoglobulin G κ (IgG κ) immunoglobulin and the variable antigen-binding region of the murine anti-IL6 antibody. CNTO 328 has a long half-life (approximately 2 weeks) without significant immunogenicity and hence may be more beneficial clinically relative to BE-8. It also has a high affinity for recombinant as well as native IL-6. This feature enables it to inhibit the binding of IL-6 to the IL-6R, resulting in the blockade of the IL-6/IL-6R/gp130 signal transduction pathway and, subsequently, antitumor and anti-inflammatory activities.[31,93,108] CNTO 328 has been for a phase II multicenter trial in multiple myeloma. In addition to BE-8 and CNTO 328, several fully human McAb or humanized McAb to IL-6 have also been developed, including CNTO 136 and ALD518.[109] These IL-6 antibodies have been evaluated in clinical trials in patients with rheumatoid arthritis and systemic lupus erythematosus.[109]

Targeted IL-6 as a potential clinical therapy for cancer

CNTO 328 also shows promise for ovarian cancer in clinical trials.[110] In this trial, the primary endpoint was response rate as assessed by combined RECIST and CA125 criteria. One patient of eighteen evaluable had a partial response, while seven others had periods of disease stabilization. In patients treated for 6 months, there was a significant decline in plasma levels of IL-6-regulated CCL2, CXCL12, and VEGF. Gene expression levels of factors that were reduced by CNTO 328 treatment in the patients significantly correlated with high IL-6 pathway gene expression and macrophage markers in microarray analyses of ovarian cancer biopsies. The investigators noted that the percentage of women who received clinical benefit from CNTO328 is an unusually high proportion for an experimental cancer drug study. Typically, only 5–20% of participants secure any benefit from taking untried treatments, according to the investigators.[110] In a phase I/II study of CNTO 328 in metastatic renal cell cancer, the results showed CNTO 328 was well tolerated overall, with no maximum tolerated dose or immune response observed. CNTO 328 stabilised disease in >50% of progressive metastatic renal cell cancer patients with one partial response was observed.[111] In a phase I study of prostate cancer patients, no adverse events related to CNTO 328 treatment were observed. Patients treated with CNTO 328 showed with higher levels of apoptosis markers. Following a single dose, serum concentrations of CNTO 328 declined in a biexponential manner. The study also showed a decrease in pStat3 and p44/p42 mitogen-activated protein kinases. In addition, gene expression analyses indicate down-regulation of genes immediately downstream of the IL-6 signaling pathway and key enzymes of the androgen signaling pathway.[112] In a trial for patients with metastatic castration-resistant prostate cancer who received prior docetaxel-based chemotherapy, treatment with CNTO 328 plus mitoxantrone/prednisone was well tolerated, although improvement in outcomes was not demonstrated.[113] In another phase II trial of CNTO328 in chemotherapy-pretreated patients with castration-resistant prostate cancer, treatment of CNTO 328 resulted in a PSA response rate of 3.8% and a RECIST stable disease rate of 23%. Despite evidence of CNTO-mediated IL-6 inhibition, elevated baseline IL-6 levels portended a poor prognosis.[114] These clinical trial results highlight the fact that the efficiency of CNTO 328 based strategy may be improved in combination with other chemotherapy agents.

Antibody targeted IL-6 therapy using BE-8 or CNTO 328 has also been applied in clinical trials in patients with lymphoma, myeloma, renal cell carcinoma, Castleman disease, and B-lympho-proliferative disorders.[108,115] Improved performance status and amelioration of fever in patients without serious adverse effects have been observed.[108] Clinical trials using BE-8 to treat HIV-1-positive patients with immunoblastic or polymorphic large cell lym-

Table 2
Recent and on-going trials with the anti-IL-6 signaling drugs.

Agent	Target	Disease	Refs.
CNTO 328	IL-6	Ovarian cancer Renal cell cancer Prostate cancer Castleman disease	110–115
BE-8	IL-6	Lymphoma Multiple myeloma	107,116
Tocilizumab	IL-6R	Arthritis Castleman disease Crohn's disease Oral cancer	23, 117–121
Jak inhibitor	Jak	Myeloproliferative neoplasms Psoriasis	122–125

phoma showed that antitumor activity was not only limited and inconsistent but also associated with side effects of reduced platelet count.[116] A combination therapy of BE-8, DXM and high-dose melphalan, followed by autologous stem cell transplantation, has been shown to significantly inhibit IL-6 activity in advanced MM patients without toxic or allergic reactions.[107] However, side effects of increased incidence of thrombocytopenia and neutropenia were observed.[107] Clinical studies have shown that the inhibition of IL-6 signaling by Tocilizumab is therapeutically effective in rheumatoid arthritis, juvenile idiopathic arthritis, Castleman's disease, and Crohn's disease.[117–121] Therapies strictly targeting IL-6R using Tocilizumab are effective in treating oral squamous cell carcinoma through inhibiting angiogenesis.[23] However, there is yet no evidence showing whether it is a better strategy to inhibit the IL-6 ligand or block the IL-6R completely. In a phase I study in patients with Castleman's disease, eighteen (78%) of 23 patients (95% CI, 56% to 93%) achieved clinical benefit response (CBR), and 12 patients (52%) demonstrated objective tumor response. The overall results suggest that CNTO328 is an effective treatment with favorable safety for the management of Castleman's disease.[115] Recently, inhibitions of IL-6 signaling through different Jak inhibitors have been reported in the treatment of myeloproliferative neoplasms and psoriasis.[122–125] (Table 2)

Conclusions

The increasing knowledge regarding the molecular biology mechanisms of IL-6 and its interrelations to human cancer will lead to the development of novel antibody based therapies. New IL-6 target treatments not only target malignant tumor cells, but also target the interactions of cancer cells with their microenvironment. Extensive studies have identified IL-6 as a crucial part of tumor cell survival, proliferation, migration and drug resistance (Fig. 1, Table 1). The identification of novel IL-6 antibodies in the laboratory is followed by rationally designed clinical trials that validate these antibodies, either as a single agent or in combination with other chemotherapy drugs. During the last decade, several McAbs that inhibit IL-6 activity in preclinical models have been developed, with promising results both in cancer cell lines and animal models. Further investigations in xenograft tumor models are needed for predictions of the therapeutic efficacy of IL-6 McAbs. In addition, several of the IL-6 McAbs and IL-6 downstream protein small molecule inhibitors are now undergoing phases I and II clinical trials, which will continue to establish the therapeutic efficacy of anti-IL-6 therapy in human cancer (Table 2).

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