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# Interleukin-6 Cytokine: A Multifunctional Glycoprotein for Cancer

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## Abstract

Interleukin 6 is a multifunctional cytokine. Its increased levels have been associated with elevated cancer risk, and also these levels have been found to be a prognostic factor for several cancer types. In addition, increased levels have been found in coronary heart disease, insulin resistant patients, advance stage cancer patients, atopy/asthma and in patients with blood circulating micrometastasis. Additionally several studies with different types of cancers have been performed to identify the correlation between interleukin-6 levels, stage, treatment response and severity of symptoms. The influence of interleukin-6 is performed mainly through the janus kinase-signal transducer and activator of transcription-zinc finger protein 1-2 signaling pathway. As a result, the increased levels of interleukin-6 are responsible for enhanced neo-angiogenesis, inhibition of cancer cell apoptosis and deregulation of the control mechanisms in the microenvironment. In addition, increased levels of inteleukin-6 have been found to increase the production of collagen and a-actin which induce interstitial lung disease. In the current mini review we will present information regarding the interleukin-6 and published results in several cancer studies and finally we will comment in future treatment approaches blocking this cytokine in cancer patients.

**Keywords:** Interleukin-6; Cancer; Cytokine; Angiogenesis; JAK; STAT; SNAIL

## Introduction

Interleukin-6 (IL-6) is a multifunctional cytokine that influences the activity of cancer cells. It is a glycoprotein which consists of 184 amino acids and has 26 kilodaltons (kDa) as a molecular weight [1]. It is involved in tumor growth, malignant differentiation of cancer cells and microenvironment immunomodulation [2]. These properties are a result of enhanced neo-angiogenesis, inhibition of cancer cell apoptosis and acquired cell resistance [3]. Again these results are mediated through several signaling pathways, however; the most important ones are the transcription activator 3 and the signal transducer [4-9]. Interleukin-6 levels have been observed elevated in advanced stage cancer [10] and again elevated levels have been associated with increased risk of cancer [11,12]. Moreover; IL-6 has been found to be a cancer disease prognostic marker [13] and also it was increased in patients with cancer induced cachexia [14]. Interleukin-6 has been found overexpressed in cancer cells lines expressing epidermal growth factor receptor (EGFR) mutation [4], however; in another study further investigation of the levels of IL-6 after tyrosine kinase inhibitors (TKIs) indicated that TKIs induce apoptosis, but at the same time increase IL-6 levels [15]. During the cancer, cell apoptosis growth factors, which stimulate the IL-6 release, circulate in the extracellular matrix. The increased levels of interleukin-6 subsequently induced collagen and a-actin production and interstitial lung disease pattern was observed. In addition, there are few data whether IL-6 levels are associated with treatment effectiveness or cancer stage for patients with EGFR mutations [10]. IL-6 receptor mutation has been investigated in mice and it was observed that the animals carrying this mutation had additionally overexpression of signal transducer and activator of transcription 3 (STAT3) activities. In these animals the extent of the infiltrates was directly associated with the overexpression of the stat-3 signaling pathway [16]. Furthermore; increased levels of IL-6 have been associated with increased lung cancer risk in lifetime non-smoking women with asthma/atopy [17]. Increased levels of IL-6 have been found in patients with coronary heart disease [18] and insulin resistance has been reported from increased levels of IL-6 in a lung cancer patient [19]. Several trials have been performed investigating the IL-6 levels and the effects on the prognosis, stage, treatment outcome and cancer relapse. Regarding surgically resected patients the higher the interleukin-6 levels after the first day, the sooner was the relapse [20]. These studies can be summarized according to each cancer type as follows: a) ocular [21], b) lung EGFR mutation positive adenocarcinomas [4,15], c) colorectal [22], d) small cell lung cancer [3], e) brain [2,23], f) cancer stem cells [24,9], g) head and neck [25], h) hepatocellular [26], i) breast [27], j) melanoma [28], k) bone [29] and l) nasopharyngeal cancer cells [30].

## Search Methods

We performed an electronic article search through PubMed, Google Scholar, Medscape, and Scopus databases, using combinations of the following keywords: interleukin-6, cancer, angiogenesis, and cytokine. All types of articles (randomized controlled trials, clinical observational cohort studies, review articles, case reports) were included. Selected references from identified articles were searched for further consideration, without language limitation.

## Cancer and Metastasis

### Lung cancer

In the study by Ishiguro et al. it was observed in lung cancer cell

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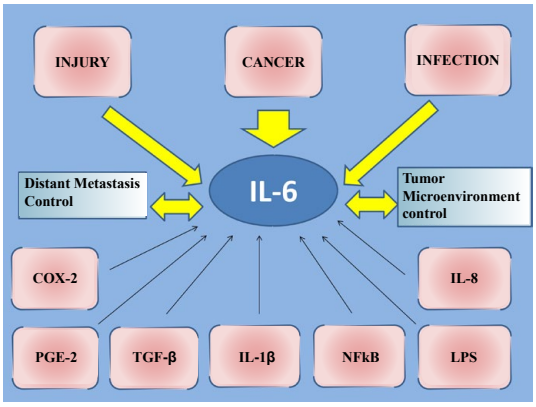
lines that administration of tyrosine kinase inhibitors was an efficient therapy for lung cancer as it increased cell apoptosis. However; it was observed that the IL-6 mRNA and IL-6 protein, IL-6 transcriptional activity and IL-6 secretion was simultaneously increased. The levels of these IL-6 parameters were closely associated with the production of a-actin and collagen. Therefore, a connection of treatment effectiveness and increased fibrotic activation has been established. In the study by Gao et. al. [4] the tyrosine-phosphorylated STAT3 signaling pathway was found to be overexpressed in cell lines harboring somatic-activating mutations in the tyrosine kinase domain of EGFR. It has also been previously observed that the pSTAT3 is found in 50% of lung adenocarcinomas. These specific cell lines had elevated IL-6 levels and blockade of IL-6/gp130/JAK pathway, which led to decrease of pSTAT3 levels. Reduction of IL-6 via RNA interference could be a future adjuvant treatment. Elevated levels of IL-2,-6 and tumor necrosis factor-α (TNF-α) have been also observed in ocular metastasis again establishing a connection between increased levels of IL-6 and metastastic activity of the primary tumor [21]. Furthermore, in the study by Wojcik et al. [3] the serum levels of IL-6, vascular endothelial growth factor (VEGF), neurone-specific gamma isozyme of enolase(NSE) and pro-gastrin releasing peptide (ProGRP)in previously untreated small cell lung cancer patients were measured. A cut off value of 5.1 ng/l was identified to be associated with increased levels of VEGF. The extent of the disease and IL-6 levels were identified as independent prognostic factors. However; the clusters: a) ProGRP and IL-6, b) ProGRP and VEGF were also identified as independent prognostic factors. Mesenchymal stem cells (MSCs) were co-cultured with lung cancer cell lines and it was observed that MSCs activate the IL6/JAK2/STAT3 signaling pathway and apart from formatting tumors in immunodeficient animals, these dual cultures demonstrated drug resistance (Figure 1). Again when the previous signaling pathway was blocked all these effects were stopped producing [9]. Moreover, cancer stem cells (CSCs) were co-cultured with lung cancer cell lines and increased expression of IL-6R gene and its ligand IL-6 were observed. In addition, as previously with the MSCs, drug resistance to methotrexate (MTX) and 5-fluoracil (5-FU) was observed. The experiment were carried out in CSCs and with non-CSCs and the previous presented results were observed only for the CSCs. Blocking the IL-6R and IL-6 with siRNA or mAbs resulted in reduced cell proliferation [24]. It has been previously observed that matrix metalloproteinase -10 (MMP-10) mRNA levels are low in tumor tissues and the MMP-10 protein is increased in the tumor. The IL-6 reduces the MMP-10mRNA levels and enhances the MMP-10 protein in lung cancer cells. Again, the pathway that regulates the IL-6 activity is the JAK2/STAT3. The STAT3 mRNA levels are increased when the cells are treated with IL-6 [6] (Table 1).




COX-2: Cyclooxygenase-2; PGE-2: prostaglandin E2; TGF-β: Tumor Necrosis Factor-β; LPS: Lipopolysaccharides; IL-1β: Interleukin-1beta; NFkB: Nuclear Factor kappa beta; IL-6: Interleukin-6

**Figure 1:** IL6/JAK2/STAT3 signaling pathway.

## Bone

The IL-6 plasma levels have an influence in several aspects of normal and pathogenic bone metabolism. Through the mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription pathway (STAT) and phosphatidylinositol-3 kinase (PI3K) signaling pathways the IL-6 is responsible for local bone inflammation control, bone remodeling, proliferation, cell survival and pre-tumor microenvironment control. It has observed that increased IL-6 levels in several cancer types attribute to early bone metastasis [29] (Table 1).

## Breast

In the study by Oh et al. [27] the transglutaminase 2 (TG2) was investigated and it was observed that its biological activity is closely related to that of IL-6 and subsequently to tumor aggressiveness. In a breast cancer cell lines with knocked down TG2 and IL-6 experiments were carried out and increased distant hematogenous metastasis and low distant metastasis free survival (DMFS) were correlated when IL-6 and TG2 were combined as a cluster (Table 1).

## Hepatocellular

In the study by Wang et al. [26] estrogen either endogenous or by exogenous administration were observed to have a protective role against metastasis from hepatocellular cancer by reducing the levels of IL-6 and hepatocellular growth factor (HGF). An experiment was carried out in rats, which were divided it into four groups. It was observed that in the group, which had ovariectomy (OVX), a 60% metastasis was observed to the lungs. On the other hand, only 17-25% of metastasis was observed in the other 3 groups. In conclusion, the microenvironment is controlled and these two factors are suppressed (Table 1).

## Head and Neck

The properties of IL-6 have been investigated in the epithelial mesenchymal cells (EMT). Stable overexpression of IL-6 or recombinant IL-6 in immortalized oral epithelial cells (IOE) and CAL27 cells induce the expression of mesenchymal marker, vimentin and silmutaneouslysupress E-cadherin through the janus kinase-signal transducer and activator of transcription-3-zinc finger protein 1-2 (JAK/STAT4/SNAIL) signaling pathway. Knockdown of STAT3 by inhibition of the focal adhesion kinase activation (FAK) reverses the influence of IL-6 in tumorigenic activities. In addition, it was observed that the pre-malignant environment is again control by IL-6 also in lymph nodes. Therefore again the local concentration of IL-6 in lymph nodes is a possible marker for early disease recurrence. The EMT tumorigenic process could be possibly identifying in lymph nodes with state of the art diagnostic equipment such as; endobronhcial ultrasound biopsy (EBUS) or esophageal ultrasound (EUS)[25]. In the study by Zhang et al. [30] reported that IL-6R (receptor) overexpression in addition with IL-6/STAT3 signaling facilitates malignant transformation of nasopharyngeal premalignant cells (NPC). In addition, through this couple of NPCs malignant properties are enhanced (Table 1).

## Brain

In the study by Kim et al. [23] several factors affecting the microenvironment such as: a) IL-1, b) IL-3, c) IL-6, d) tumor necrosis factor-α(TNF-α), e) TNF-β, f) insulin like growth factor-1 (IGF-1),

| Author | Cancer | Subjects | Results | Reference |
|---|---|---|---|---|
| Zhang Y et al. | Lung | 271 Patients; VATS vs. OT surgery | IL-6;-8;-10 measured in POD 1 and POD 3. Lower IL-6 and IL-10 plasma levels are associated with less immunosuppression in VATS surgery | [31] |
| Kita H et al. | Lung | 107 patients. Surgery | IL-6 in days POD 0; 1 and 2. P-stage and IL-6 levels in POD 1 were independent prognostic factors for early lung cancer recurrence | [20] |
| Tawara K et al. | Bone metastasis | Review | IL-6 as a bone remodeling cytokine; cancer cell proliferation; local bone inflammation | [29] |
| Yadav A et. al. | Head and Neck | *In vitro* | IL-6 mediate epithelial-mesencymal transition in head and neck cancer cells by increasing their metastatic potential | [25] |
| Zhang G et. al. | Nasopharyngeal | *In vitro* | IL-6R overexpression coupled with enhanced IL-6/STAT3 signaling facilitates malignant transformation of NPC cells | [30] |
| Kim S-H et. al. | Human lung adenocarcinoma; astrocytes | *In vivo* | Rapamycin modulates brain microenvironment; increases IL-1;-3;-6; TGF-α;TGF-β; PDGF; MCP-1; MIP-1; IGF-1 | [23] |
| Seike T et. al. | Human lung adenocarcinoma; astrocytes | *In vivo* | MIF; IL-6;-8; IL-1β; PAI-1; TNF-α.<br>Astrocytes are activated by tumor cellfactors | [2] |
| Ishiguro Y et. al. | Tongue cancer HSC-3 and lung cancer A549 cell lines | *In vitro* | TKI therapy increases cell apoptosis and increases a-actin and collagen | [15] |
| Gao S-P et. al. | Lung adenocarcinomas | *In vitro* | Pan-JAK inhibitor (P6) blocked activation of STAT3 | [4] |
| Valles S-L et al. | Melanoma | *In vitro- In vivo* | IL-6; stress hormones and glutathione regulate metastasis | [28] |
| Oh K et. al. | Breast | *In vitro* | TG2 and IL-6 in combination compose a cluster for DMFS survival | [27] |
| Wang Y-C et. al. | Hepatocellular | *In vivo* | Estrogen have the ability to suppress metastasis by reducing levels of IL-6 and HGF | [26] |
| Koh E et. al. | Lung cancer | patients | Tumor postoperative stage; tumor size; IL-6 staining in tumor tissue and IL-6 plasma levels are predictive survival factors | [32] |
| Ujiie H et. al. | Lung cancer | Patients | IL-6; HGF and NNMT preoperatively are prognostic indicators for stage III NSCLC undergoing surgery and chemotherapy | [13] |
| Wojcik E et. al. | Lung cancer | Patients | IL-6; NSE; VEGF;platelet count and proGRP are prognostic factors | [3] |
| Hsu H-S et. al. | MSCs | *In vitro- In vivo* | MSC increase the IL6/JAK2/STAT3 pathway | [9] |
| Yi H et. al. | CSCs | *In vitro- In vivo* | CSCs exibit increased IL-6R gene expression and increased production of its ligand IL-6 | [24] |
| Zhang X et. al. | Lung cancer | *In vitro* | IL-6 controls MMP-10 through JAK2 and STAT3 signaling pathway | [6] |
| Pine SR et. al. | Lung cancer | Patients | IL-6; IL-8; CRP.<br>Only IL-8 is an early lung cancer biomarker | [11] |

IL-6: Interleukin-6; POD: Postoperative Day; OT: Open Thoracotomy; VATS: Video Assisted Thoracic Surgery; IL-10: Interleukin-10; IL-6R: Interleukin-6 Receptor; STAT3: Signal Transducer And Activator Of Transcription 3; NPC: Nasopharyngeal Cancer Cells; TNF-A: Tumor Necrosis Factor-A; IL-1: Interleukin-1; IL-8: Interleukin-8; IL-10: Interleukin-10; PDGF: Platelet Derived Growth Factor; IGF-1: Insulin Like Growth Factor-1; MIP-1: Macrophage Inflammatory Protein-1; TNF-B: Tumor Necrosis Factor-B; TKI: Tyrosine Kinase Inhibitor; PAI-1: Plasminogen Activator Factor; MCP-1:Chemoattractant Protein-1; HGF: Hepatocyte Growth Factor; JAK: Janus Kinase; TG2: Transglutaminase 2; DMFS: Distant Metastasis Free Survival; NNMT: Nicotinamide N-Methyltransferase; NSCLC: Non-Small Cell Lung Cancer; NSE:Neurone-*Specific* Gamma Isozyme Of *Enolase*; VEGF: Vascular Endothelial Growth Factor; MSC: Mesenchymal Stem Cells; CSC: Cancer Stem Cells; CRP: C-Reactive Protein; MMP-10: Matrix Metalloproteinase; Progrp: Pro-Gastrin Releasing Peptide

**Table 1:** Interleukin-6 cancer studies

g) macrophage inflammatory protein-1 (MIP-1), h) chemoattractant protein-1 (MCP-1), i) platelet derived growth factor (PDGF) were investigated in a brain metastasis model. It was observed that IGF-1, which is responsible for activating and maintaining local inflammation, was reduced in correlation with all other parameters, which were increased. Rapamycin is a lipophilic drug, which has the ability to penetrate the blood brain barrier (BBB), and could be possibly used for local microenvironment control. It could with further studies and investigation bea future neo-adjuvant treatment for several cancer types. In the study by Seike et al. [2] IL-6,-8, IL-1β, TNF-α, plasminogen activator factor (PAI-1) and migration inhibitory factor (MIF) were evaluated in a human lung brain metastasis model with astrocytes. It was observed that different cancer cell cultures mediate the microenvironment and each inflammatory factor is differently regulated depending on the different group of cancer cells, in any case, the astrocyte behavior is mediated by tumor cell factors (Table 1).

## Melanoma

A model where stress hormones, IL-6 and glutathione (GSH) regulate the metastasis growth has been proposed in a melanoma study [28]. It has been observed that IL-6 activates GSH, which is a cell protective molecule against free radicals. Three stress related hormones (corticosterone, noradrenaline and adreno-corticotropin hormone ACTH)) were evaluated in comparison to IL-6 and metastasis growth. The hormone levels were mediated by the circadian rhythm. It was observed that corticosterone and noradrenaline at increased levels increased subsequently the production of IL-6. A mechanism of tumor metastasis has been proposed where IL-6 induces ACTH release, which in turn increases the release of IL-6 from metastatic cancer cells. GSH is released from the liver and tumor γ-Glutamyltranspeptidase (GGT) degrades plasma GSH (Table 1).

## Surgery

The interleukin plasma levels have been investigated in correlation with the surgery outcome. In specific, in early lung cancer patients the interleukins IL-6, IL-8 and IL-10 plasma levels were measured in the post-operative day 1 (POD 1) and 3 (POD 3) between two type of surgeries: a) open thoracotomy (OT) and b) video-assisted thoracic surgery (VATS). It was observed that in VATS operation, lower levels of IL-6 and IL-10 were observed in days POD 1 and POD 3. This is a result of a less invasive surgery procedure, since more cytokines are released in the OT surgery procedure and the healing process is also longer [31]. In another study by Kita et al. [20] 107 early lung cancer patients were evaluated with IL-6 in the POD days 0, 1 and 2. The mean follow-up was 18.1 months. The results of the plasma measurements indicated that the P-stage and IL-6 values of the POD 1 were significant independent factors for early disease recurrence. In the study by Koh et al. [32] tumor size, IL-6 plasma levels, positive immunohistochemical staining for IL-6 and postoperative stage were observed to be predictive factors for overall survival. Moreover, in the study by Ujiie et al. [13]

the increased levels of IL-6, hepatocyte growth factor (HGF) and nicotinamide N-methyltransferase (NNMT) levels preoperatively were observed to be a prognostic indicator for the survival of patients with stage III non-small cell lung cancer undergoing surgery and chemotherapy (Table 1).

### IL-6 targeted treatment

Targeting the signaling pathway of the IL-6 is a novel target. The tissue inhibitor of metalloproteinase-3 (TIMP-3) is a possible target. It has been previously observed that low TIMP-3 and high IL-6 levels patients had lower survival [33]. The novel (2E,5E)-2,5-bis(4-(3(dimethylamino)-propoxy) benzylidene) cyclopentanone (A13) has been observed to reduce nitric oxide (NO), TNF-α, HGF and IL-6. In addition, it reduces damages to the lung and reduced pain in several induced inflammatory models [34]. Neutralizing IL-6 antibodies have been used to block the JAK1-STAT3 signaling pathway in a lung cancer model [5]. Tocilizumab an anti-IL-6R antibody has been used and apart from reducing the lung cancer tumorigenic activities it was also observed to reduce the cancer related cachexia [14]. Toll like receptor 2 is a novel molecule under consideration as a future immunomodulatory therapy for targeting tumor inflammation. Previous positive results have been published in a melanoma model [35]. Moreover, another novel IL-6R blocker which is under investigation is siltuximab [36]. This novel agent has been used also in combination with docetaxel chemotherapy [37]. The IL-6R antibodies will be soon replaced by nonantibody-based inhibitors called avimers. Their main advantage is that they do not induce allergic reactions and have more prolonged activity in comparison to the antibodies (> two weeks). Currently the AMG-220 is being developed by AVIDA [38].

## Discussion

Inflammation cytokines such as: a) C-reactive protein, b) IL-6 and IL-8have been identified as lung cancer markers. Increased plasma levels of these cytokines have been associated with increased for risk lung cancer [39,12,11]. However, only IL-8 has been identified as an early lung cancer biomarker (more than 2 years whereas IL-6 for <2 years) [11]. Also in never smokers, different polymorphisms of inflammatory pathway genes are also related with increased lung cancer risk, especially IL-6, IL-1β and IL-1RN [40]. Increased levels of IL-6 have been observed in advanced stage cancer in several cancer types [41]. Caregivers of cancer patients with advanced stage lung cancer have also high levels of IL-6 and other inflammatory markers, which are reduced when the cancer patient is treated efficiently [41]. A joint effect of asthma/atopy and IL-6 gene polymorphism in lung cancer has been identified in lifetime non-smoking Chinese women [17]. The IL-6 levels have been also associated with coronary heart disease and efforts have been made to target the IL-6 receptor as a treatment for coronary heart disease [18]. Moreover, IL-6 levels have been identified as a marker for EMT malignant transition in lymph nodes [25]. Insulin allergy and immunologic insulin resistance has been identified in a patient with lung cancer in the pre-chemotherapy period. In specific due to excessive IL-6 plasma levels >96.4 pg/ml (reference range <4 pg/ml) local skin irritation (erythema) was observed in the site of insulin administration and the HbA1c levels were deregulated. In addition, increased IgG anti-insulin antibodies were observed. All the excessive laboratory parameters return to normal after chemotherapy initiation [19].

Moreover, different pro-inflammatory and fibrogenic cytokines have been investigated in correlation to radiation induced lung toxicity (RILT) and it was observed that low pretreatment levels of IL-8 were correlated with the development of RILT. In addition, if IL-8 and TGF-β1 levels were combined, then an independent prognostic cluster was formed for RILT development [42]. Increased levels of IL-6, collagen and a-actin have been found after TKI inhibitor treatment in lung cancer cell lines and tongue cancer HSC-3 cells. The treatment efficiency was associated with the fibrogenic activity [15]. Again in the study by O`Donoghue in interstitial fibrosis patients elevated levels of IL-6 were correlated with overexpression of STAT3 signaling pathway and enhanced fibrogenic activity. Therefore, fibrotic lesions are expected when IL-6 levels are elevated; however, no clear association has been made between the levels and extent of the lesions. There is however literature for stage IIIB and IV lung cancer patients regarding their treatment response and IL-6 serum levels. It has been observed that increased levels of circulating IL-6 are a prognostic factor for poor treatment response [10]. The raltitrexed, which is a specific thymidylate synthase inhibitor when administered in colorectal cancer patients with or without chemotherapy activated a cascade of cytokines and chemokines and the identification of infection in these patients was impossible. Again, we would like to have data regarding the fibrogenic activation in these patients with radiologic findings [22]. Neutralizing IL-6 antibodies are on the market and they have been observed to reduce cancer related cachexia [14]. However, we would like to have a study with sleep disturbances and IL-6R antibody treatment. Regarding the factors that are mediated by IL-6 in several cancer types, we can summarize them to the following. a) Multiple myeloma (MyC regulator gene, STAT3, fibroblast growth factor (FGFR))[43], b) lung cancer (EGFR, STAT3) [4], c) colon cancer (STAT3, c-Myc) [44], d) prostate cancer (IGF-1R, Human Epidermal Growth Factor Receptor 2 (Erb2)) [45], e) breast cancer (Notch, Rat sarcoma (Ras), Human Epidermal Growth Factor Receptor 2 (HER2)) [46], f) ovarian cancer (Stat3, VEGF) [47] and g) bladder cancer nuclear factor *kappa*-light-chain-enhancer of activated *B* cells (Nf-kappaB) [48].

Finally, the immune system has a dual role, it can either enhance the tumor growth and tumor metastasis, however, it can also protect the body from carcinogenesis and metastasis [49]. Therefore, a balance is necessary since not all cytokines are responsible for enhancing the tumor microenvironment and tumor activities.

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