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Review Article

IL-6 Activities in the Tumour Microenvironment. Part 1

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Abstract

The predominant role of IL-6 in cancer is its key promotion of tumour growth. IL-6 binds IL-6 receptor (IL-6R) and the membrane-bound glycoprotein gp130. The complex I-6/IL-6R/gp130 starts the Janus kinases (JAKs) and signal transducer and activator of transcription 3 (STAT3) or JAK/STAT3 pathway. IL-6R exits in two forms: a membrane-bound IL-6Rα subunit (mIL-6R) that participates in classic signalling pathway and soluble IL-6R subunit (sIL-6R) engaged in trans-signalling. The pro-tumour functions of IL-6 are associated with STAT3, a major oncogenic transcription factor that triggers up-regulation of target genes responsible for tumour cell survival. IL-6 combined with TGF-β induces proliferation of pathogenic Th17 cells. The anti-tumour function of IL-6 is the promotion of anti-tumour immunity. IL-6 trans-signaling contributed to transmigration of lymphocytes in high endothelial venules (HEV). Dendritic cell (DC) secreted IL-6 in the lymph node influences the activation, distribution and polarisation of the immune response. Elevated serum levels of IL-6 and increased expression of IL-6 in tumour tissue are negative prognostic marker for patients' survival.

Introduction

The cytokine interleukin-6 (IL-6) is a member of a group of cytokines that possess a four-helical structure [1]. It was described first as a B cell differentiation factor in 1986 [2], [3], [4]. IL-6 has various biological activities such as stimulation of the growth of tumour cells of murine plasmacytoma and human myeloma [5]. IL-6 also has an inhibitory effect on the antiviral antibody response [6]. Moreover, IL-6 is produced by several types of cells such as monocytes, macrophages, Kupffer cells [7], keratinocytes, endothelial cells, B cells and T cells [1].

The intracellular signaling is induced when the complex of IL-6 and IL-6 receptor (an 80-kDa ligand-binding chain IL-6Rα, CD126) binds the membrane glycoprotein 130 (gp 130) (a signal-transducing chain, IL-6Rb, CD130) [8], [9] that initiates the Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) or JAKs / STAT pathway [8]. IL-6R is found in two forms, a transmembrane form mIL-6Rα, and a soluble form sIL-6R. IL-6 binds to both of these forms and subsequently interacts with the gp 130 to trigger downstream signal transduction and gene expression [7]. The gp130 lacks an intrinsic kinase domain, and therefore the members of the JAKs family, like JAK1, JAK2 and tyrosine kinase 2 (Tyk2), are linked to gp130 [5]. The complex of IL-6, IL-6R and gp130 phosphorylates the afore-mentioned kinases and later activates the cytoplasmic transcriptional factors as STAT1 and STAT3 [10]. Therefore, IL-6 activates transcriptional factors through IL-6R/gp130 complexes with following downstream effects [5].

The membrane-bound IL-6Rα subunit is located on the membrane of target cells. The second receptor subunit is the gp130 associated with mIL-6Rα/IL-6 that subsequently activates the "classic signaling pathway" [11]. The complex IL-6 / mIL-6Rα

leads to dimerisation of gp130 and subsequent activation and phosphorylation of STAT3 via JAK. The classic signalling is realised during the early immune responses and activates acute-phase proteins like C-reactive protein (CRP) [9]. This “classic signalling” is accomplished on cells, expressing both the mIL-6R subunit and gp130 subunit. The latter is widely expressed, but the former is found only on hepatocytes, leukocytes and megakaryocytes [5], [9].

The second mechanism of induction of intracellular reaction is when IL-6 associates with soluble IL-6R (sIL-6R) and binds gp130 on cellular membranes that do not express mIL-6Rα. That process is defined as “trans-signalling” an alternative of classic signalling [12]. The presence of sIL-6R in the serum is a result of shedding of the mIL-6R from the cellular membranes induced by apoptosis and realised through a dis-integrin and a metalloproteinase 10 (ADAM10 or ADAM17) [13]. A second way of achieving sIL-6R is via differential splicing of IL-6 mRNA [12]. The shedding of the IL-6R is also initiated by CRP [14,15], or bacterial toxins [16]. The shedding of IL-6R is released from neutrophils at the beginning of the inflammatory process [9]. The presence of sIL-6R and IL-6 induces Th17 cells and is responsible for the balance between Th17 and T regulatory cells (Tregs) [17]. Therefore, IL-6 trans-signaling modulates the T cell response [18]. IL-6 trans-signalling is observed in many cell types such as epithelial cells, neutrophils, macrophages and T cells [9] and that the complex of IL-6 with the sIL-6R is associated with the cellular membrane gp130 [19] (Figure 1).

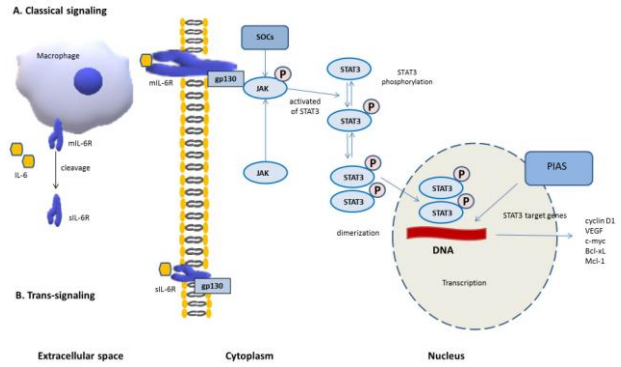

Figure 1: IL-6/JAK/STAT3 signaling; A) Classical-signaling: IL-6 binds to mIL-6 R, and interplays with membrane gp 130; B) Trans-signaling: sIL-6R cleaved from macrophage membranes binds to IL-6 and then the complex interplays with membrane gp130; Then the complex IL-6 / IL-6R / gp130 triggers the activation of JAK, and meanwhile the suppressor of cytokine signalling (SOCS) acts on JAKs and stops phosphorylation of gp130, STATs and the JAKs themselves. STAT3 (an oncogenic transcriptional factor) is activated by JAKs, phosphorylated and formed dimers (pSTAT3-pSTAT3). The dimerised pSTAT3 complex moves to nucleus and pSTAT3 complex trigger transcription of STAT3 target genes (cyclin D1, VEGF, c-myc, etc) through interaction with DNA. Cancer promotion is initiated. The protein inhibitors of activated STATs (PIAS) can suppress the transcription of STAT3 target genes

IL-6 up-regulates several acute-phase proteins such as CRP, fibrinogen, etc. [15], and IL-6 has both anti- and pro-inflammatory activities [9]. The anti-inflammatory functions are realized by the complex IL-6/mIL-6R and include activation of STAT3, followed by intestinal cell proliferation, inhibition of epithelial cell apoptosis and release of acute-phase proteins [19], [20]. The pro-inflammatory activities are realized by the complex IL-6 / sIL-6R and include activation of the immune system through recruitment of mononuclear cells (myeloid-derived suppressor cells – MDSC and macrophages), inhibition of T cell apoptosis and down-regulation of Treg differentiation [17], [21] (Figure 2).

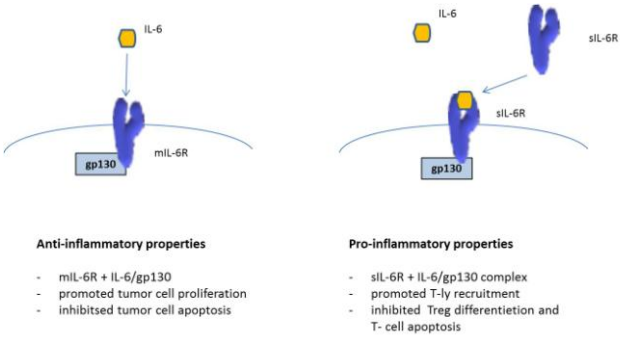

Figure 2: The dual role of IL-6 signalling: IL-6 classical signalling with anti-inflammatory properties and IL-6 trans-signalling with pro-inflammatory properties

During chronic inflammation, IL-6 induces proliferation of Th17 cells and inhibits the differentiation of Tregs [11]. The predominant cell type that secreted IL-6 during acute inflammation is monocyte/macrophage and in chronic inflammation – T lymphocyte [22]. IL-6 is also produced by endothelial cells, B cells, T cells, fibroblasts and some tumour cells [1]. IL-6 can be secreted by stromal fibroblasts in a mouse model of gastric cancer [23].

Colon tumours usually have a decreased expression of membrane-bound IL-6R in comparison to normal epithelial colon tissue. Nevertheless, the expression of ADAM17, associated with shedding of the IL-6R, is increased in tumours, and therefore the “trans-signalling” pathway is involved in colon carcinogenesis [24], [25].

Interleukin-6 and cancer development

Pro-tumour functions of IL-6

The predominant role of IL-6 in cancer is the promotion of tumour growth. The interaction of IL-6 and its receptor-activated JAKs with following induction/activation of STAT3 through tyrosine phosphorylation and subsequent transcription of target genes [9] is vital in cancer formation. In turn, IL-6 induces IL-6-dependent STAT3 activation, resulting in up-regulation of genes that promote the survival of cancer cells [26]. The target genes responsible for

tumor cell survival (Bcl-2, survivin, Mcl-1), [27] proliferation (c-Myc, Cyclin D1, Cyclin B) [28], angiogenesis (VEGF) [29], metastasis (MMP2, MMP9) [30], [31], cell adhesion (ICAM-1, TWIST1), inflammation (IL-6, IL-17, IL-23, Cox2), and others [32]are influenced by IL-6 activities.

STAT3 is a major oncogenic transcription factor that is activated by the binding of IL-6 to the IL-6 receptor [25]. The first event is the binding of IL-6 to mIL-6R followed by gp130 dimerisation and trans-phosphorylation of STAT3 through tyrosine phosphorylation. Subsequently, STAT3 trans-locates to the nucleus in epithelial tumour cells, where STAT3 dimers bind DNA and modulate the expression of some target genes [22], [33]. Additionally, the IL-6 / STAT3 pathway blocks the maturation of dendritic cells (DCs), inhibits T cell activation [34] and maintains immunosuppression through MDSC and macrophages (tumour-associated macrophages – TAMs) [35].

IL-6 is also involved in the differentiation of monocytes to macrophages, downregulates apoptosis of T lymphocytes, and the production of Th2 cytokines [3], [36], [37].

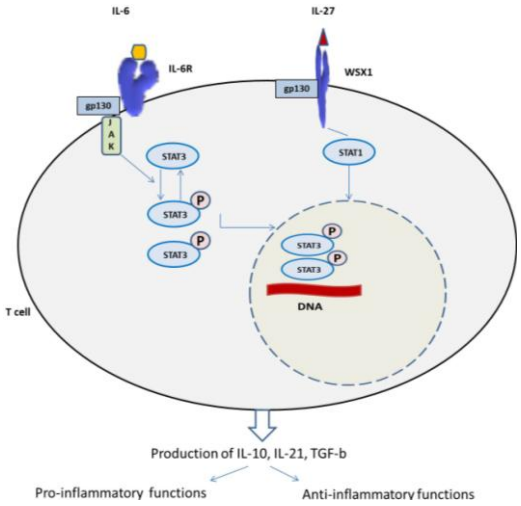

Figure 3: IL-6 and IL-27 trigger a common signal transduction pathway in T cell

Several molecules secreted by tumour cells, including IL-1β, TNF-α, IL-6 and TGF-β are considered to be promoters of Th17 differentiation from naïve CD4+ T cells. There exists evidence that Th17 cells increase in number in the tumour microenvironment (TME) [38]. In contrast, IFN-γ and IL-4, the main cytokines involved in Th1 and Th2 polarisation, respectively, negatively regulate Th17 differentiation [25], [38]. The pro-inflammatory cytokines, IL-6 and TNF-α, are produced in *TME* mostly by hematopoietic cells and also by tumour cells. They are tumour-promoting and further enhance nuclear factor kappa B (NF-kB) and STAT3 activation [39,40]. Moreover, IL-6 and IL-27 mediate signal transduction through STAT3 and STAT1 activation of Th17 and Treg differentiation [48]. IL-6 combined with TGF-β3 or TGF-β1 induce proliferation of pathogenic Th17 cells [42]. IL-6 and IL-27 both can initiate common signal transduction pathways in T cells [41] (Figure 3).

STAT3 is an essential activator for Th17 cell proliferation [43], and on the other hand IL-6, a STAT3 activator, together with TGF-β increased the expression of main transcription factors RORα (human) and RORγt (mouse) for Th17 cell induction and IL-17 production [44], [45]. In contrast to STAT3 activation, STAT1 activation inhibits the development of Th17 cells [46]. Cytokines like IL-27 and IFN-γ are involved in the inhibition of Th17 development in a STAT1-dependent manner [5], [46]. Another cytokine that inhibits Th17 cells development is IL-2 in a STAT5 manner [47]. Therefore, the STAT family transcription factors, via the action of various cytokines, exert positive or negative influences on Th17 development. Interferon-regulatory factor 4 (IRF-4) exerts positive effect on Th17 cell appearance [48] and T-bet negatively influence the development of Th17 cells [49]. Treg helpers are mainly naturally occurring thymus-derived Tregs (nTregs) and TGF-β-induced Tregs (iTregs) [17]. Also, iTregs generate from naïve T cells in the periphery, after stimulation with TGF-β [50]. There are other T cells with regulatory functions including the CD8+ Tregs, Tr1 cells, and Th3 cells [51]. The balance between Th17 cells and Tregs is controlled by IL-6 that maintains immune homeostasis. TGF-β is important for Th17 and Treg cells differentiation, and it induces both Foxp3 and RORγt expression [52]. Therefore, IL-6 is considered to be a pro-inflammatory cytokine that promoted Th17 cell differentiation and inhibits Tregs development. The cytokine IL-17 has dual roles in TME, having pro- and anti-tumour activities [53] (Figure 4).

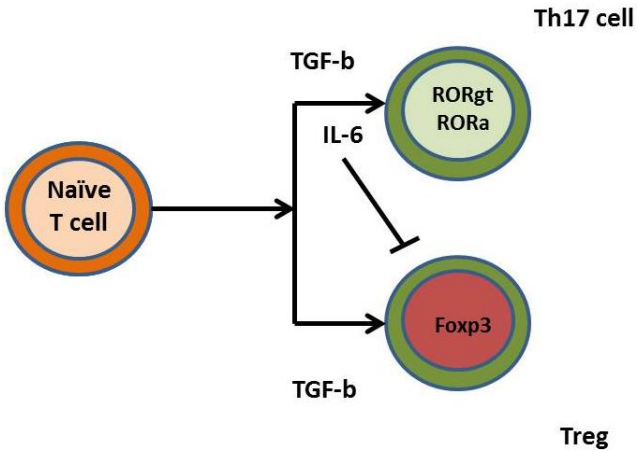

Figure 4: IL-6 maintains Th17/Treg balance. IL-6, together with TGF-β triggers Th17 differentiation from naïve T cells. On the other hand, IL-6 alone inhibits Treg differentiation triggered by TGF-β itself

IL-6 is a growth factor for human colon cancer cells, and inhibition of IL-6 signalling interferes with the growth of tumour cells [24]. In TME tumour-infiltrating lymphocytes (TILs) produce elevated levels

of pro-tumorigenic cytokines such as IL-17A, IL-17F, IL-21, IL-22, TNF-α and IL-6 [40]. Some of the cytokines like IL-6 and TNF-α are also produced by tumour cells [20]. Colorectal cancer (CRC) cell lines - DLD-1 and HT-29, are affected by IL-6, TNF-α and IL-17 cytokines, and result in enhanced NF-kB and STAT3, which induce colorectal cancer cell growth [40].

IL-6 plays a major role in promoting proliferation of tumour cells and in inhibiting apoptosis via binding to IL-6Rα to the gp130. Following activation of JAK / STAT signalling pathway [54] namely of STAT1 and STAT3 [55] cancer initiation and proliferation occurs. Similarly, to TNF-α, IL-6 supports tumour development by induction of normal epithelial cells to convert into cancer stem-like cells [56]. STAT3 can mediate nuclear translocation of β-catenin. The nuclear co-expression of pSTAT3 and β-catenin is associated with poor survival of colon cancer patients [57]. IL-6 initiates tumorigenesis by hypermethylation of tumour suppressor genes or by hypomethylation of retrotransposon long interspersed nuclear element-1 (LINE-1) in oral squamous cell cancer [58]. IL-6 is a powerful (relevant) angiogenic factor, and its high levels correlate with that of VEGF in colorectal cancer [59,60]. Moreover, IL-6 initiates VEGF action in gastric cancer [61]. The secretion of IL-6 and subsequent STAT3 phosphorylation up-regulate some angiogenic mediators such as VEGF, VEGFR2 and neuropilin 2 [62].

In conclusion, IL-6 in the TME supports tumour development, metastasis and evasion from the effective anti-tumour immune response.

Anti-tumour functions of IL-6

The main anti-tumour function of IL-6 is the promotion of anti-tumour immunity [63], [64]. The analysis of many specimens of human tumours reveals that the immune contexture, defined by the type of immune cells, their activity, and distribution mainly in the invasive front, is a better prognostic factor as compared to histological staging and grading [63]. There is evidence that IL-6 trans-signalling is important in the initiation of T cell immune responses [65], [66]. Using trans-signalling IL-6 is a key cytokine in the modulation of anti-tumor immune response [67]. IL-6 maintains anti-tumour immunity at two main sites: first in the lymph nodes where lymphocyte priming takes place and second in tumour nests where IL-6 promotes the recruitment of effector T cells in TME [68].

In lymph nodes, dendritic cells (DCs) encounter tumour antigens. Also, naïve T cells and memory T cells enter lymph nodes through high endothelial venules (HEV). The polarisation interacts with the naïve T cells and initiates T cell polarisation [69], [70]. DCs secrete IL-6 in the lymph node that influences the activation, distribution and polarisation of the immune response [71].

In HEV, IL-6 trans-signaling acts on T lymphocytes to initiate tethering and rolling on the endothelial surface of HEV. Later the interaction between CCL21 on endothelial cells and CCR7 chemokine receptor on T lymphocytes initiates the chemokine activation that helps firm adhesion. The lymphocyte firm adhesion molecule 1 (LFA-1) binds to intercellular adhesion molecule 1 or 2 (ICAM-1 or ICAM-2) on endothelial cells and lymphocyte trans-endothelial migration in HEVs in lymph nodes or the tumour site [70], [72], [73]. IL-6 trans-signaling contributes to L-selectin-mediated and transmigration of lymphocytes to HEV [74]. Usually, tumour vessels had tortuous structure and express low levels of trafficking molecules such as ICAM-[66], [67]. Endothelial cells of tumour vessels and cancer-associated fibroblasts are the main producers of IL-6 at tumour sites [74]. Thus, injection of H-IL-6 induces high IL-6/sIL-6Rα concentration in TME. IL-6 trans-signaling increases CD8+ T cells trafficking into tumours and supports adoptive T cell transfer in adoptive cell therapy [67]. In mouse models the administration of H-IL-6 or application of systemic thermal therapy before adoptive CD8+ T cell transfer leads to enhanced tumour cell apoptosis and delay of tumour cell growth [67], [74].

The anti-tumour activities of IL-6 trans-signalling are used as basis for anti-tumour therapy. Thermal therapy is based on enhanced lymphocyte recruitment as response to febrile temperatures about 39.50 for periods up to 6 hours [66], [75]. The thermal stress leads to transient decrease in lymphocyte count with following increase of it in cancer patients with subsequent tumour restriction [76], [77].

Thermal therapy up-regulates gp130 on the endothelial cells in tumour microvessels [78] and thus supports IL-6/sIL-6Rα activity with following CD8+ T cell trafficking and recruitment into the tumour site [74], [78]. Taken together, the administration of H-IL-6 or thermal therapy could restrain cancer development when combined with adoptive CD8+ T cell vaccination [67], [78], [79].

Elevated levels of IL-6 and other serum biomarkers in cancer patients

Various biomarkers for the initiation and development of cancer exist. These biomarkers are associated mainly with inflammation and obesity [15], [80]. Chronic inflammation is related to colon carcinogenesis [68], [81]. It has been reported that cancer-associated inflammation determined disease progression and survival in CRC [82].

The existing meta-analysis shows that serum CRP and IL-6 levels could be associated with the risk of CRC development [33], [83], [84] but this is not useful for identifying colorectal adenomas [85]. TNF-α serum levels were studied in the risk of CRC

development [86]. Another investigation report increased mRNA level of IL-6 that is predictive for colorectal cancer development with distant metastases [87]. Several CRC case-control studies show increased serum levels of CRP, TNF-α, IL-6 and IL-8 in colorectal adenoma and CRC patients [88]. Moreover, expression-enhancing polymer-phisms in the genes for IL-6, TNF-α, IL-1β and IL-8 are associated with increased risk for the development of colorectal cancer [89]. The increased release of IL-6 in the sera of CRC patients is associated with CEA-induced production of IL-6 by Kupffer cells, macrophages, lymphocytes and tumour cells [90]. Serum IL-6 > 10 pg/ml values are associated with higher incidence of CRC with distant metastasis and therefore can be an independent, negative prognostic marker for patients' survival [91].

Adipose tissue is considered to be the largest endocrine tissue that secrets various cytokines such as IL-2, IL-6, IL-8, TNF-α, etc. [92]. IL-6 is a poor prognostic factor in obese patients with CRC [93], [94], [95], [96].

Clinical significance of tissue overexpression of IL-6 in CRC cancer tissue

Few studies address the immunohisto-chemical expression of IL-6 in CRC [97], [98], [99]. Some studies show overexpression of IL-6 in tumour tissue in glioblastoma [94], prostate cancer [43], renal cell cancer [57], gastric cancer [61] etc. Additionally, the expression of IL-6R and gp130 was investigated in tumour cells of CRC [97]. The overexpression of IL-6 in cancer tissue correlates to advanced stage, lymph node metastasis, and venous invasion [100], [101]. Therefore, IL-6 cancer cell expression can be a relevant marker of cancer progression.

In conclusion, IL-6 is mainly a pro-tumorigenic cytokine that triggers JAK / STAT3 activation with subsequent promotion of tumour cell growth and suppression of tumour cell apoptosis. IL-6 / STAT3 signalling regulates the balance between Th17 and Tregs in TME with immunosuppressive properties. The anti-tumour activity of IL-6is associated with modulation of T cell polarisation initiated by IL-6 secreting DCs and with the support of T lymphocyte recruitment in lymph nodes. A further investigation is necessary to elucidate the intimate mechanisms of IL-6 regulation.

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