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IL-6 Family Cytokines: Key inflammatory mediators as biomarkers and potential therapeutic targets

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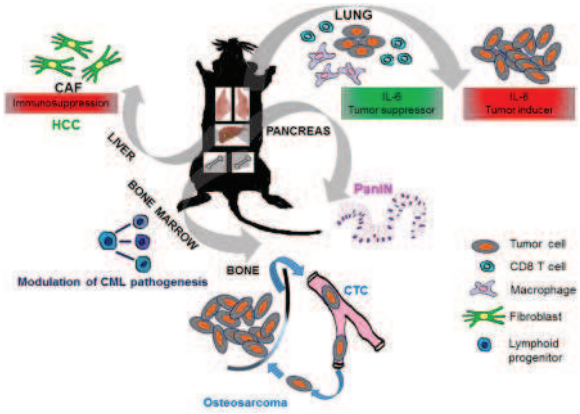
Abstract

IL-6 is a critical cytokine in acute phase response and involved in the pathogenesis of several chronic inflammatory diseases including cancer. Studies have highlighted that levels of IL-6 and its family members can be useful for diagnosis, prognosis of relapse-free survival and recurrence. IL-6 family cytokines have been identified as cancer biomarkers through screening of inflammatory mediators in different fluids including saliva, serum, and bronchoalveolar lavage fluid (BALF). IL-6 can be modulated by chemopreventive drugs, small molecules, monoclonal antibodies and immune checkpoint inhibitors. Unveiling the different sources of IL-6, the interaction between IL-6 and its cellular targets, the IL-6-dependent tumor resistance mechanisms, and the identification of novel regulators of IL-6 are some of the highly complex topics included in this review and their understanding could aid cancer biomarkers and therapy development.

Graphical abstract



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Conflicts of interest statement

None.

Keywords

IL-6; IL-6 family; cytokine; cancer biomarker; immunoprevention

1. Introduction

Inflammation, one of the hallmarks of cancer, is a known contributor to cancer initiation and progression [1]. The role of IL-6 in the development and progression of inflammation-associated cancers has been widely described. Several cells in the tumor microenvironment are capable of secreting IL-6, including epithelial oncogenic cells as well as stromal cells including immune cells [2]. Besides its direct effect on tumor cell proliferation, IL-6 is also a major immunomodulatory agent, playing active roles in the regulation of acute phase reactions, activation of T helper cells, inhibition of T regulatory (Tregs) cells and differentiation of B cells by orchestrating innate and adaptive immune responses [3]. Dual roles for IL-6 have been described in some specific tumors as it is the example of lung cancer in which IL-6 has a preventive role in the tumor initiation but it is also capable of enhancing cancer progression [4] [5].

IL-6 monoclonal antibody (Siltuximab) has been tested in mouse xenografts models of lung cancer and it has tumor inhibitory effect particularly potent when cancer-associated fibroblasts were coadministered, suggesting that IL-6 secreted by the stroma might be more susceptible to the antibody effect [6]. Cancer associated fibroblasts (CAF) in hepatocellular carcinoma (HCC) also secrete high levels of IL-6 which contributes to tumor progression via recruitment of immune cells with immunosuppressive phenotype. This data suggests that IL-6 blockade in addition to immune checkpoint inhibitors may potentially overcome the immune-checkpoint inhibitor resistance in some types of cancer [7]. The gp130 f/f (IL6st) knock-in mouse model exhibits hyper activation of the STAT3 arm of IL6. When this transgenic mouse is crossed with Kras(G12D) mice to study lung tumorigenesis, an increase in atypical adenomatous hyperplasia, adenocarcinoma in situ, and invasive adenocarcinoma throughout the lung are observed, suggesting that IL-6 trans-signaling can be a target for the treatment of KRAS-driven lung adenocarcinoma [8].

2. Identification of IL-6 family cytokines as cancer biomarkers

2.1. IL-6

The IL-6-type family cytokines are IL-6, IL-11, IL-31, Cardiotrophin-1, Ciliary neurotrophic factor (CNTF), Cardiotrophin-like cytokine (CLC), Granulocyte-colony stimulating factor (G-CSF), Leptin, Leukemia inhibitory factor (LIF), Neuropoietin and Oncostatin M. The main cellular source of IL-6 is monocytes and T cells but it can also be produced by other cells including epithelial cells [9]. IL-6 promotes Th17 cells development when combined with TGF-β [10], inhibits TGF-β-induced Treg differentiation [11], plays a role in neutrophil and macrophage recruitment and is also associated with the pathogenesis of chronic inflammatory disease [12]. IL-6 activates STAT3 through two pathways: classical and trans-signaling. Classical signaling of IL-6 occurs in cells expressing IL-6Rα and it induces anti-inflammatory molecules [12]. On the other hand, trans-signaling is possible in

all cells expressing gp130 and causes pro-inflammatory cytokines induction which drives chronic inflammation. IL-6 not only contributes to cancer related inflammation but also plays crucial roles in DNA damage repair, anti-oxidant defense system, proliferation, invasion, metastasis, angiogenesis and metabolic remodeling [12] (Figure 1).

Screening of cytokines can serve to identify immunological response-related soluble factors which may be increased in cancer even at early stages. A study that included 224 hepatocellular carcinoma (HCC) cases and 644 controls revealed that higher serum levels of IL-6 are predictive of increased HCC risk, independently of hepatitis virus infection, radiation exposure and lifestyle-associated factors [13]. IL-6 can also be involved in stemness and metastasis via its downstream target, Osteopontin, in HCC. Plasma levels of IL-6 and Osteopontin were found to be independent prognostic factors for HCC patients [14].

Serum levels of IL-6 have been associated with tumor progression. In bladder cancer, IL-6 serum levels were found to be remarkably higher in patients with recurrence compared to non-recurrent patients [15]. In pancreatic ductal adenocarcinoma (PDAC), serum levels of IL-6 can be useful as diagnostic biomarker and this cytokine has also been implicated in the progression of this type of tumor [16]. It has also been reported as a useful classifier for the identification of high-risk stage I lung adenocarcinoma patients [17]. In addition to serum based studies of inflammatory mediators, tissue microarray and immunohistochemistry analysis of IL-6 in human cervical cancer tissues suggest its usefulness as prognostic biomarker as well as potential therapeutic targets for treatment of cervical cancer [18]. Advanced or metastatic colorectal cancer patients with high serum IL-6 levels had poorer overall survival (OS), progression-free survival (PFS) and anti-VEGF resistance [19] than patients with lower levels. In addition to solid tumors, elevated serum levels of IL-6 can serve as a biomarker in hematological malignancies like Hodgkin's lymphoma [20]. IL-6 and the JAK-STAT3 signaling pathway have also been found upregulated in myeloproliferative neoplasms (MPN). Interestingly, the recent JAK1/2 inhibitor trials in MPNs demonstrated that lessening inflammation can be even more helpful that targeting mutations [21].

Besides serum levels, Il-6 detection in saliva has been proposed as a useful diagnostic biomarker of cancers like oral squamous cell carcinoma (OSCC) [22]. In OSCC, IL-6 modulates resistance to radiation by inhibiting oxidative stress through the Nrf2-antioxidant pathway [23].

2.2. IL-6 as a critical inflammatory marker in murine models

IL-6 is the most highly elevated cytokine in COPD-like inflammatory mouse model and is required for lung cancer promoted by COPD-like inflammation [24]. IL-6 differently modulates both tumor initiation and progression via activating STAT3 in a mouse model of lung cancer induced by the Kras oncogene. It suppresses lung cancer initiation via sustaining lung homeostasis, modulating lung macrophages and activating cytotoxic CD8+ T cells under Kras oncogenic stress, and on the other hand it promotes lung cancer cell growth by promoting the cell proliferation regulator Cyclin D1 [4]. In a different lung cancer mouse model, $Ccsp^{Cre/+}$ $Kras^{LSL\text{-}G12D/+}$ (CC-LR), IL-6 and IL-6 class cytokine LIF were highly

detected in BALF from mice with tumors. Chemopreventive treatment of mice with *myo-inositol* diminished IL-6 and phospho-STAT3 signaling, a process likely mediated by tumor associated macrophages [25].

In the pancreas, $Kras^{G12D}$ activation induces premalignant lesions called pancreatic intraepithelial neoplasias (PanINs). IL-6 trans-signaling-dependent activation of Stat3/Socs3 is required to promote murine PanIN progression to PDAC [26]. In a similar fashion, IL-6 has been described as a critical tumor booster during early colitis-associated cancer (CAC). Its production by myeloid cells in the lamina propia has a protective role on normal and premalignant intestinal epithelial cells (IECs) against apoptosis [27].

IL-6 has also been found increased during the development and malignant progression of astrocytomas [28]. Although suppression of IL-6 does not influence preneoplastic astrogliosis, it prevents tumor formation in a spontaneous GFAP-v-$src^{+/-}$ mouse astrocytoma model. In a murine model of osteosarcoma, tumor progression and recurrence are modulated by IL-6 via promoting tumor self-seeding by CTCs [29].

In murine models of hematological malignancies such as CML, increased IL-6 levels were detected in BCR/ABL transgenic mice. IL-6 produced by myeloid CML cells inhibits lymphoid differentiation from multipotent progenitor cells [30] and shapes the CML pathogenesis.

Apart from tumor cells derived IL-6 secretion, mesenchymal stem cells (OvMSC) can secrete IL-6 which contributes to tumor progression in models like ovarian cancer. Coinjection of OvMSC with ovarian cancer cells enhances ovarian tumor development in NOD-SCID mice [31]. In a murine model of hepatocellular carcinoma (HCC), IL-6 is predominantly expressed by CAFs creating an immunosuppressive environment via up-regulation of inhibitory immune checkpoints [7] (Figure 2).

A study of gastric tumorigenesis in mice challenged with N-methyl-N-nitrosourea demonstrated the importance of IL-6 in driving tumor development through STAT3 stimulation by using IL-6 knockout mice [32]. Inoculation of another chemical carcinogen, diethylnitrosamine (DEN), remarkably increased serum interleukin-6 (IL-6) concentration in males compared to females. Estrogen-mediated suppression of IL-6 production by Kupffer cells diminished liver cancer risk in females in the DEN-induced hepatocellular carcinoma mouse model [33], suggesting that suppression of IL-6 abrogates the gender differences in hepatic carcinogenesis.

2.3. IL-11

IL-11 was identified as a 19 kDa soluble factor belonging to the IL-6 cytokine family in the supernatant of bone-marrow derived stromal cell. The main cellular source of IL-11 are bone, connective tissue, and malignant cells [34]. Through transmembrane protein glycoprotein-130 beta subunit, IL-11 shows pro-tumorigenic activities such as proliferation, self-renewal, invasion and angiogenesis [34]. In a prospective cohort of 60 smokers including patients with lung cancer, COPD and both, IL-11 was found to be a specific biomarker for the diagnosis of lung adenocarcinoma in BALF specimens [35].

Although there is a limitation with cohort size and short follow-up time, IL-11 has been found to be a useful biomarker for diagnosis and prognosis in patients with pancreatic cancer [36]. Assessment of IL-11 expression by immunohistochemistry in clear-cell RCC (ccRCC) has demonstrated its association with increased risk of recurrence and poor survival for ccRCC patients with early-stage disease. As a result of immunohistochemical evaluation of tissue microarrays including paired tumor/peritumoral liver tissue from 290 patients who had undergone hepatectomy for histologically proven HCC, intra-tumoral IL-11 is significantly concordant with higher tumor node metastasis (TNM) stage and has been found to be an independent prognostic factor for progression-free survival (PFS) [37], [38].

2.4. Oncostatin M

Oncostatin M (OSM) is produced by monocytes, macrophages, T cells, neutrophils and dendritic cells. Oncostatin M plays fundamental roles in heart remodeling, inflammation, hematopoiesis, liver regeneration and cancer [39]. OSM levels are associated with inflammatory response-genes, epidermal growth factor (EGF) signaling and epithelial-to-mesenchymal transition (EMT) in human estrogen receptor (ER)-negative/human epidermal growth factor receptor 2 (HER2)-negative breast cancer [40]. High expression of OSM and OSM receptor (OSMR) mRNA have been associated with reduced ER and progesterone receptor (PR) protein levels in a cohort of 70 invasive breast cancers [41]. OSM stimulates the expression of *ZEB1*, Snail (*SNAI1*), and *OSMR* as well as the CSC phenotypes in pancreatic cancer, suggesting that therapeutic targeting of the OSM/OSMR axis could be useful for patients with PDAC [42]. Analysis of serum diagnostic biomarkers in PDAC showed that OSM was overexpressed in PDAC patients versus controls (AUC=0.744). OSM could also be a predictive biomarker for treatment of PDAC response to drugs like gemcitabine and erlotinib [43].

2.5. IL-31

IL-31 is mainly expressed by circulating Th2 lymphocytes and skin-homing CLA^+ $CD45RO^+$ T cells. IL-31 binds its heterodimeric receptor formed from IL-31RA and the OSMR chains and this leads to phosphorylation of Jak1/2, which in turn, triggers phosphorylation of STAT1/3/5 or PI3K/AKT. These pathways promote skin inflammation, development of T cell type-2 inflammation in asthma and allergic rhinitis as well as gut inflammation. Elevated serum levels of IL-31 contribute to the pathogenesis of different tumor types including endometrial, lung cancer, cutaneous T cell lymphoma, follicular B cell lymphoma [44] [45]. Expression of IL-31 was found to be increased in patients with mastocytosis compared with those seen in healthy control subjects ($P < .0473$) [46].

3. Identification of IL-6 family cytokines as potential cancer treatment target

3.1. IL-6

Activation of IL-6/STAT3 pathway has been reported in various cancer types. Blockade of IL-6/STAT3 has been targeted by potent chemopreventive drugs. As an example, disulfiram, targets cancer stem cells [47] and STAT3 signaling in triple-negative breast cancer [48]. Targeting STAT3 could cause elimination of cancer stem-like cells and contribute to

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