Immune-suppressive effects of interleukin-6 on T-cell-mediated anti-tumor immunity

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Accompanied by the growing clinical applications of immunotherapy in the treatment of cancer patients, development of novel therapeutic approaches to reverse the immune-suppressive environment in cancer patients is eagerly anticipated, because the success of cancer immunotherapy is currently limited by immune-suppressive effects in tumor-bearing hosts. Interleukin (IL)-6, a pleotropic proinflammatory cytokine, participates in tumor cell-autonomous processes that are required for their survival and growth, and is therefore known as a poor prognostic factor in cancer patients. In addition, an emerging role of IL-6 in modulating multiple functions of immune cells including T cells, dendritic cells, and macrophages is responsible for the dysfunction of innate and adaptive immunity against tumors. Therefore, the IL-6-targeting approach is of value as a promising strategy for desensitization and prevention of immune-suppressive effects, and should be an effective treatment when combined with current immunotherapies. The aim of the present review is to discuss the immune-suppressive aspects of IL-6, notably with modification of T-cell functions in cancer patients, and their relationship to anti-tumor immune responses and cancer immunotherapy.

KEYWORDS
cancer immunotherapy, immune suppression, interleukin-6, T cell, Th1

1 | ANTI-TUMOR IMMUNE RESPONSES AND IMMUNE-SUPPRESSIVE MECHANISM

Over the past decade, the importance of cancer immunotherapies typified by vaccinations with TAA plus adjuvants or antigen-presenting DC,1,2 immune-checkpoint blockade,3,4 and adoptive transfer of tumor-specific T cells including T cells that express engineered...
exogenous TCR or CAR, has been acknowledged to have clinical relevance. These immunotherapies potentially activate anti-tumor immune responses mediated through tumor-specific CD8$^+$ and CD4$^+$ T cells, NK cells, NKT cells, and DC. CD8$^+$ T cells primed with TAA exert anti-tumor activity after differentiation into CTL. Activated CD4$^+$ T cells also differentiate into more diverse subsets of effector helper T cells including IFN-γ-producing Th1, IL-4-producing Th2, IL-17-producing Th17, and Tfh in the context of in vivo environments. These effector cells further give rise to long-lasting memory T cells that are required for a durable response against the tumor.

However, measurable numbers of patients do not induce beneficial immune reactions systemically or at local tumor sites when the immunotherapies are given. One of the most problematic concerns in efficient T-cell-based cancer immunotherapy is a tumor-induced immune-avoiding environment in cancer patients that comprises tumor-initiated immune-suppressive factors and cells such as Treg, MDSC, and M2 macrophages. These immune-suppressive components abolish the function of both immune-stimulatory cells (such as DC) and responder cells (such as tumor-specific T cells). Functional depression of immune-stimulatory DC is a critical problem to be solved especially in vaccination with TAA, because of inadequate T-cell-mediated adaptive immunity. In contrast, tumor cells express several molecules that induce T-cell tolerance or exhaustion. Treatment with Abs against the immune-checkpoint molecules, most notably CTLA-4 and PD-1/PD-L1, gives rise to therapeutic benefits through the reversal of the exhausted phenotype of primed T cells and their reprogramming into functional effector T cells. Moreover, in the case of adoptive T-cell transfer, it is possible that the immune-suppressive environment dampens efficient secondary responses of transferred T cells and their long-term survival after encountering TAA in recipients. Therefore, abrogation of the detrimental immune suppression in tumor-bearing environments has now emerged as one of the primary approaches for therapeutic improvement. For this purpose, it is necessary to explore the immune-suppressive mechanisms by which tumor and stroma cells, immune cells, and their related cytokines and metabolites lead to functional deficiency in tumor-specific T cells. Here, we focus on the immune-suppressive aspect of IL-6 in tumor-bearing mice and cancer patients.

### 2 | IL-6 SIGNALING AS A POOR PROGNOSTIC FACTOR

Chronic inflammation is recognized as a tumor hallmark that is implicated in tumorigenesis and tumor progression. IL-6, one of the proinflammatory cytokines, is involved in cancer progression. Systemically elevated levels of IL-6 have been observed in patients with various types of cancer such as renal cell carcinoma, melanoma, ovarian, colorectal, and head and neck cancer, or in patients with cachexia or wasting syndrome. Of note, IL-6 is known as a poor prognostic factor because elevated levels of IL-6 are inversely proportional to survival rates of cancer patients. For a long time, the main focus has been on the direct effects of IL-6 signaling to tumor cells through at least three major signaling pathways: JAK2/STAT3, Ras/MAPK, and PI3K/Akt cascades, which are attributed to expansion and survival of tumor cells, neo-angiogenesis, and inflammation.

The pro-tumorigenic role of IL-6 in cancer patients is complex because IL-6 exerts multiple effects not only on tumor cells, and its action is mediated in autocrine and paracrine ways. In addition to tumor cells, IL-6 can be secreted from myeloid cells such as macrophages, DC, and MDSC, and other tumor-associated stroma such as cancer-associated fibroblasts, endothelial, or senescent cells. These cells collaborate with tumors to establish an environment that amplifies spatial and temporal availability of IL-6 signaling in tumor-bearing animals (Figure 1).

Generally, IL-6 binds with a heterotrimeric surface receptor consisting of IL-6Ra and signal-transducing component, gp130. However, even in cells lacking surface IL-6R expression, a soluble form of IL-6R (soluble IL-6R; sIL-6R) can mediate IL-6 signaling termed as "IL-6 trans-signaling" through the formation of functional multi-molecular complexes of IL-6/sIL-6R with membrane-bound gp130. In addition to IL-6, elevated levels of sIL-6R have been proposed as a poor prognostic factor in patients with certain types of cancer, because they promote IL-6 stabilization and amplify IL-6 signaling through protecting IL-6 from rapid degradation in vivo. IL-6R is produced by the shedding of membrane-bound IL-6R via proteolytic cleavage mainly in hepatocytes or myeloid cells under inflammatory conditions. This finding was supported by the clinical observation that lower expression of membrane-bound IL-6R on tumor-infiltrating myeloid cells was correlated with poor prognosis, because lower expression of membrane-bound IL-6R was likely to reflect the shedding and release of sIL-6R from CD14+ myeloid cells.

### 3 | IMMUNE-MODULATORY EFFECTS OF IL-6 SIGNALING ON T CELLS

Accumulating evidence for tumor cell-extrinsic activities of IL-6 signaling on normal cells, particularly involving detrimental effects on anti-tumor immunity, has been raised. Direct action of IL-6 has been evidenced by STAT3 activation in CD4$^+$ T cells and myeloid cells, and their activation was diminished by IL-6 blockade, implying that these cells are attractive targets for IL-6-mediated immune regulation in tumor-bearing mice and cancer patients. Our group and others demonstrated using different models that IL-6 blockade significantly improved the differentiation of CD4$^+$ T cells into IFN-γ-producing effector Th1 cells in tumor-bearing mice in response to immunotherapies such as DC vaccination or immune-checkpoint blockade. Targeted deletion or specific inhibition of sIL-6R also rescued the attenuation of Th1 differentiation. Thus, systemically increased IL-6/sIL-6R in tumor-bearing hosts is responsible for the impaired Th1 responses which are often observed in cancer patients. Consistently, data from TCGA indicate a clear association of increased IFN-γ expression in the tumor microenvironment with improved overall survival. In contrast, IL-6/sIL-6R signaling is predisposed to redirect the differentiation of CD4$^+$ T cells into IL-4-
producing Th2-like cells. These observations also accord with clinical data indicating that dominant Th2 cytokine profiles in patients are associated with unfavorable outcomes. Moreover, numerous studies have shown that under some circumstances such as autoimmune diseases, IL-6 suppresses the development of TGF-β-induced Treg and in turn facilitates the differentiation into RORγt+Th17 or CXCR5+Tfh cells which can be beneficial in anti-tumor immune responses. However, in tumor-bearing mice, IL-6 blockade did not alter the expression of classical transcription factors dictating differentiation of Th1/Th2 subsets (T-bet, GATA-3), nor the frequencies of NOS3-Treg, RORγt-Th17, or CXCR5+Tfh cells which can be beneficial in anti-tumor immune responses. Indeed, in tumor-bearing mice, IL-6 blockade did not alter the expression of classical transcription factors dictating differentiation of Th1/Th2 subsets (T-bet, GATA-3), nor the frequencies of NOS3-Treg, RORγt-Th17, or CXCR5+Tfh cells. Although the functional requirement of STAT3 for IL-6-mediated Th1 inhibition has been shown, the roles of other components, IL-6-mediated ERK or PI3K activation in modulating Th1 differentiation, remain to be investigated. In addition, although IL-6-mediated up-regulation of suppressor of cytokine signaling 1 has been shown to inhibit IFN-γ receptor/STAT1-dependent Th1 differentiation in vitro, in vivo roles of these signaling components remain unclear.

**FIGURE 1** Interleukin (IL)-6 signaling forms a pro-tumorigenic immune-suppressive network. Tumor cells supply and receive the IL-6 signal in an autocrine way. Tumor-initiated qualitative changes in immune cells have been further implicated in IL-6 production from myeloid-derived suppressor cells (MDSC), dendritic cells (DC), and fibroblasts/endothelial cells. IL-6 inhibits the maturation of DC, and promotes the generation of immune-suppressive alternatively activated (M2) macrophages and regulatory DC. These compromise the activation/priming of tumor-specific T cells. In addition, IL-6 dampens Th1 differentiation of CD4+ T cells, which decreases their ability to help CD8+ T cells and DC, resulting in impaired adaptive immune responses to the tumors. IL-6 stimulates the production of immune-suppressive factors such as IL-10, prostaglandin E2 (PGE2), and vascular endothelial growth factor (VEGF) by myeloid cells. These IL-6-mediated events not only weaken the innate immune responses, but also promote tumor vascularization by acting cooperatively with tumor-associated fibroblasts/endothelial cells. Through mutual interactions among these cells, IL-6 exacerbates the immune-suppressive network in tumor-bearing hosts. IFN, interferon

**4 | CONSEQUENCE OF IL-6-MEDIATED DYSFUNCTION OF CD4+ T CELLS IN TUMOR IMMUNITY**

Recent comprehensive analysis highlighted a crucial role of CD4+CD69+T-bet+CD44+CD62lowCD27lowCD90hi effector Th1 cells in effective anti-tumor immunity and in patient survival. Indeed, an adoptive transfer of tumor-specific activated CD4+ T cells led to regression of melanoma in patients. The potent anti-tumor activity of CD4+ T cells is mainly a result of their helper activity for CD8+ T cells. CD4+ T cells can trigger the production of IL-12 and other cytokines from DC through ligation of CD40 with their CD40 ligand. Moreover, T-cell-derived IFN-γ up-regulates MHC-I and -II expression and promotes presentation of TAA by DC. This mutual interaction strongly fosters the recruitment of CD8+ T cells into draining lymph nodes through the IL-12-dependent CCR5-CCL3/4 axis and/or IFN-γ-inducible chemotaxis by CXCR3-CXCCL9/10/11 interactions, which facilitates the activation of tumor-specific CD8+ T cells. Indeed, we demonstrated that although the activation and cytokine production of CD8+ T cells was not directly affected by IL-6, CD8+ T cells were not efficiently primed and activated to be functional anti-tumor effectors because of the inadequate helper activity of IL-6-sensitized CD4+ T cells, resulting in a failure of tumor elimination.

**5 | PLEIOTROPIC IMMUNOMODULATORY EFFECTS OF IL-6 SIGNALING IN MYELOID LINEAGE CELLS**

The immune-suppressive action of IL-6 could also occur at the level of myeloid cells. IL-6/STAT3 signaling directs myeloid cells to...
produce immune-suppressive molecules such as VEGF and arginase that help tumor cells escape from immune surveillance.\textsuperscript{39,40} IL-6 conversely inhibits the expression of MHC-II, CD80/86, and IL-12 in DC\textsuperscript{41} or re-programms the differentiation into IL-10-producing regulatory DC.\textsuperscript{21} These immune-suppressive effects on myeloid cells consequently compromised their ability to trigger the activation of Th1 cells and CTL.\textsuperscript{30,40} Furthermore, IL-6 promotes differentiation into M2 macrophages,\textsuperscript{39} which also amplify the immune-suppressive effects, and limit the anti-tumor T-cell responses (Figure 1). From a different perspective, it is very likely that Th2-biased differentiation of IL-6-sensitized CD4\textsuperscript{+} T cells contributes to the skewing toward the pro-tumorigenic M2 macrophages through IL-4 production.\textsuperscript{42} Consequently, IL-6 serves as a critical factor that mediates a mutually interrelated immune-suppressive loop among T cells, myeloid cells, and tumor cells to exacerbate tumor progression (Figure 1). This supports the notion that dysregulated inflammation in cancer patients is favorable to tumor progression.

### 6 | INFLAMMATION-PRONE ENVIRONMENTS TEND TO BE IMMUNE-SUPPRESSIVE

Tumor progression is greatly contingent on inflammatory status altered by inherent physical conditions.\textsuperscript{11,25,32} It is conceivable that T-cell-mediated anti-tumor immunity is affected not only by tumor-initiated immune suppression, but also by local or systemic environmental cues such as elevated IL-6. In healthy young adults, the concentration of IL-6 is quite low or undetectable. However, a circulating level of IL-6 of over 5-10 pg/mL is considered abnormally elevated,\textsuperscript{26} which is observed under several environmental conditions such as chronological aging,\textsuperscript{25,32} obesity,\textsuperscript{11} and fever-range thermal stress.\textsuperscript{43}

Elderly patients represent a large population of cancer patients and the numbers are expected to increase over the next decades. Thymic involution with aging, subsequent quantitative decrease of de novo supply, and qualitative dysfunction of T cells are responsible for the age-associated decrease in T-cell immunity.\textsuperscript{44,45} In addition to T-cell intrinsic dysfunction,\textsuperscript{44-46} age-related increases in IL-6 (referred to as inflamm-aging\textsuperscript{25,32}) should be taken into consideration in the effectiveness of T cells to eliminate tumors. Excessive increase of IL-6 in aged mice actually attenuated Th1 differentiation and, in contrast, augmented IL-4/IL-21/IL-10 production from tumor-specific CD4\textsuperscript{+} T cells, which limited their ability to provoke anti-tumor immunity (Figure 2).\textsuperscript{32} IL-6 also depressed IFN-\gamma-induced CXCR3 expression in tumor-specific T cells, leading to defective recruitment of T cells to reactive lymph nodes and tumor sites.\textsuperscript{32,38} Furthermore, considering the importance of CD4\textsuperscript{+} T cells in establishment of memory responses in durable anti-tumor immunity,\textsuperscript{2} IL-6-mediated defective CD4\textsuperscript{+} T-cell responses may also contribute to the depression of de novo memory response in aged hosts.\textsuperscript{46}

Especially in terms of the expression of transcription factors, altered T-cell responses in aged mice were associated with an IL-6-dependent gene signature, at least by c-Maf up-regulation in CD4\textsuperscript{+} T cells.\textsuperscript{32} c-Maf is up-regulated by IL-6,\textsuperscript{47} which induces IL-4/IL-21 production that are direct targets of c-Maf.\textsuperscript{48} Suppressive properties of IL-4 and IL-21 in Th1 development\textsuperscript{49} support the finding that IL-6-mediated Th1 inhibition in aged mice was partly regulated through IL-4/IL-21 production from CD4\textsuperscript{+} T cells (Figure 2).\textsuperscript{32} Furthermore, c-Maf dysfunction reversed Th1 inhibition, and redirected the

**FIGURE 2** Increased baseline risk of interleukin (IL) signaling is a potential cause of dysfunction in T-cell immunity and decreases the responsiveness to cancer immunotherapies. When young individuals are given immunotherapy, both CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells are likely to differentiate into T helper cells (Th1) and CTL to eliminate the tumor. However, IL-6 is systemically increased with aging in humans (upper right panel) and in mice.\textsuperscript{32} The excessive level of IL-6 attenuates Th1 differentiation through c-Maf up-regulation and IL-4/IL-21 production. Impaired Th1 differentiation results in inefficient anti-tumor activities of CTL (right panel). Therefore, increased baseline of IL-6 level in elderly or obese individuals is one of the possible risk factors for lower responsiveness to cancer immunotherapies and subsequent poor clinical outcomes (left panel). CXCR3, chemokine (C-X-C motif) receptor 3; IFN, interferon
function of tumor-specific CD4+ T cells from immune-suppressive to immune-activating, and augmented their anti-tumor effects in aged mice (Figure 3; Tsukamoto H. et al unpublished data). Moreover, another group demonstrated that c-Maf impeded the anti-tumor response of CD8+ T cells through induction of an exhausted phenotype in tumor tissues, emphasizing the causative role of c-Maf in tumor-promoting T-cell dysfunction. In contrast to c-Maf up-regulation, T-bet was down-regulated in CD4+ T cells primed in aged mice in an IL-6-independent way. Such integrated expression profiles of transcription factors that were affected not only by IL-6 but also by other aged environmental cues seem to result in a biased differentiation into pro-tumorigenic T cells. Widespread acceptance of immunotherapies is hindered by predictive imprecision of their therapeutic efficacy as a result of the heterogeneity of immune-suppressive/inflammatory profiles in patients with diverse physical backgrounds. Increased baseline risk of IL-6 signaling in aged or obese patients is expected to be responsible for the dysfunction in T-cell immunity, which thereby decreases the susceptibility to cancer immunotherapies (Figure 2).

Recent studies have highlighted that a fever, or mild passive heating of the whole body, drives the redistribution of CTL from circulation into lymph nodes and tumor sites in tumor-bearing animals. Intriguingly, under such febrile inflammatory condition or systemic thermal stress, IL-6 trans-signaling-induced MAPK activation in T cells promotes their L-selectin-mediated tethering to vascular endothelial cells. IL-6 signaling activated by thermal stresses also acts on endothelial cells of HEV to support firm adhesion by circulating T cells by ICAM-1. Eventually, these reactions enhanced the trafficking of CTL exclusively to tumor vessels and improved anti-tumor immunity. This anti-tumor activity of IL-6 is seemingly counterintuitive in light of its immune-suppressive effects, but coincides with the fact that tumor vessels with HEV characteristics as sites of inflammation are associated with increased CTL infiltration and better prognosis.

In viral infection models, IL-6-mediated enhancement of expansion and functional memory formation of T cells were also reported to exert immune-stimulatory effects. However, a functional relevance of IL-6 in the memory formation of tumor-specific T-cell responses remains to be elucidated, and thereby further intensive investigations on this subject will be required. It is noteworthy that viral infection-induced early IL-6 production is a part of acute inflammation with robust up-regulation of various other cytokines.

**FIGURE 3** Transcription factor c-Maf dampens the anti-tumor activity of CD4+ T cells. (A) Using ovalbumin (OVA) as a surrogate tumor-associated (neo-) antigen (TAA) and OVA-specific OT-II T-cell receptor (TCR) transgenic CD4+ T cells, cell-intrinsic effects of c-Maf on anti-tumor activity of CD4+ T cells were evaluated. OT-II T cells from wild-type or Ofl (loss-of-function mutant of c-Maf) background were transferred into young or aged C57BL/6 mice, and the mice were immunized by the transfer of OVA peptide-pulsed dendritic cells. (B) Six days after in vivo priming of donor OT-II cells, their differentiation status was evaluated by intracellular cytokine staining of interferon (IFN)-γ and interleukin (IL)-17A. IFN-γ-producing Th1 cells were reduced in WT but not in Ofl+ T cells in aged mice (left). IL-17A expression was not affected by c-Maf activity (right). (C) To examine the role of c-Maf activity on anti-tumor effects, these immunized mice were inoculated with luciferase/OVA-expressing melanoma (MO4) i.v. and the progression of pulmonary metastatic tumor was monitored by in vivo imaging of luciferase activity. Serum progression was significantly inhibited by Ofl+ CD4+ T cells in aged mice, suggesting that c-Maf is a key factor for the impaired anti-tumor immune-response in aged mice. Multiple comparisons were carried out by one-way ANOVA followed by Tukey–Kramer post-hoc tests. n = 4-10. **P < .01, ***P < .001. NS, not significant.
and acute-phase proteins, whereas only a limited number of cytokines are detected in low-grade chronic inflammatory environments, implying that the differential effect of IL-6 may be feasibly dictated or influenced by the type of inflammation and/or local inflammatory cues. Therefore, as well as systemic thermal stress, acute inflammation induced by infectious diseases or adjuvants with pathogen-like properties may function as a key driver to switch IL-6 from immune-suppressive to immune-stimulatory factor in the tumor microenvironment.

7 | PATH TO CLINICAL TRANSLATION TO REVERSE IMMUNE SUPPRESSION

IL-6 signaling augmented in cancer patients represents a promising therapeutic target that can be manipulated to disrupt the immune-suppressive environment. Clinical strategies for IL-6 blockade using mAbs against human IL-6 (CNTO 328 and B-E8) have been proposed over the last decade. In addition, the use of humanized anti-IL-6R Ab (tocilizumab) that can bind both membrane-bound IL-6R and sIL-6R, small inhibitory molecules for STAT3 activation such as curcumin analogs, or JAK2 inhibitors will also be likely options. To date, monotherapy with anti-IL-6 Ab in cancer patients demonstrated a partial or transient retardation of cancer cell proliferation and inflammatory responses in phase I/II trials, but did not provide a survival benefit or durable response mediated by long-lasting immune responses. However, the inhibition of IL-6/sIL-6R-mediated signaling combined with other therapeutic approaches has been the next promising subject of intense investigation, as already shown in preclinical mouse models. Encouraging this aim, recent clinical studies demonstrated that the higher level of IL-6 was significantly associated with a lower overall survival rate of cancer patients vaccinated with TAA, although IL-6 is a prognostic factor irrespective of treatment, and thus may not necessarily be predictive and unique to immunotherapy. Nevertheless, by virtue of mechanisms in which disruption of the IL-6/STAT3/c-Maf axis confers a "resetting" of the Th1/Th2 imbalance in tumor-specific CD4 T cells, simultaneously combined use of IL-6-targeting reagents that improves the quality of tumor-specific T cells can be a promising strategy for further enhancement of efficacy in current T-cell-based immunotherapies beyond their simply compensating for the quantitative decrease in T cells (Figure 4). Indeed, whereas the favorable reconstitution of anti-tumor Th1 cells was sometimes limited when PD-1 blockade was solely used, Th1 response was augmented by combined blockade of the PD-1/PD-L1 pathway and IL-6 signaling. Furthermore, it is interesting to note that tocilizumab is used to lessen the cytokine-release syndrome-related toxicities induced by infusion of CAR-expressing T cells. Detailed investigations about the beneficial effect of a combined IL-6 blockade on anti-tumor Th1 response in such an immunotherapeutic regimen are also eagerly anticipated.

Carboplatin/doxorubicin-based chemotherapy combined with IL-6/STAT3 blockade also showed a substantial activity in overcoming chemoresistance of tumors. In such situations, IL-6/STAT3 blockade could render the tumors more sensitive to chemotherapy, and lead to immunogenic cell death. Collectively, regarding the
immune responses against tumors, the blockade of IL-6/STAT3 signaling elicits immune surveillance by a dual mechanism that increases the immunogenicity of tumor cells through inducing cell death, and favors the re-skewing of the immune-suppressive microenvironment toward an immune-stimulatory state.

8 | CONCLUDING REMARKS AND OUTLOOK

In clinical trials, a substantial effort is being directed toward translating immunotherapeutic interventions into positive consequences in cancer patients. It is highly anticipated that understanding IL-6-mediated immune-suppressive mechanisms underlying down-regulation of tumor-specific T cells will help us expand a treatment window eligible for immunotherapeutic approaches combined with IL-6 blockade to control anti-tumor immune responses. Although widely varied tumor types and patient backgrounds make the picture even more complex, definitive and careful testing of such hypothetical strategies is warranted in cancer patients.

CONFLICT OF INTEREST

Authors declare no conflicts of interest for this article.

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