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New perspectives in cancer immunotherapy: targeting IL-6 cytokine family

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ABSTRACT

Chronic inflammation has been recognized as a canonical cancer hallmark. It is orchestrated by cytokines, which are master regulators of the tumor microenvironment (TME) as they represent the main communication bridge between cancer cells, the tumor stroma, and the immune system. Interleukin (IL)-6 represents a keystone cytokine in the link between inflammation and cancer. Many cytokines from the IL-6 family, which includes IL-6, oncostatin M, leukemia inhibitory factor, IL-11, IL-27, IL-31, ciliary neurotrophic factor, cardiotrophin 1, and cardiotrophin-like cytokine factor 1, have been shown to elicit tumor-promoting roles by modulating the TME, making them attractive therapeutic targets for cancer treatment. The development of immune checkpoint blockade (ICB) immunotherapies has radically changed the outcome of some cancers including melanoma, lung, and renal, although not without hurdles. However, ICB shows limited efficacy in other solid tumors. Recent reports support that chronic inflammation and IL-6 cytokine signaling are involved in resistance to immunotherapy. This review summarizes the available preclinical and clinical data regarding the implication of IL-6-related cytokines in regulating the immune TME and the response to ICB. Moreover, the potential clinical benefit of combining ICB with therapies targeting IL-6 cytokine members for cancer treatment is discussed.

INTRODUCTION

The tumor microenvironment (TME) encompasses the cellular and non-cellular compartments that support the survival and function of cancer cells. It comprises multiple cell types, including immune cells, endothelial cells, fibroblasts, adipocytes, other tissue-specific cell types, and the extracellular matrix (ECM) in which all cells are embedded. The crosstalk between tumor cells and the TME is fundamental for tumor initiation, growth, and expansion to other tissues.[1] Recently, novel therapeutic strategies have been proposed to target the TME in order to improve response to current immunotherapies.[2] In this context, inflammation is an attractive target, as it has been tightly linked with all cancer stages and is now accepted as a canonical hallmark of cancer.[3 4] Inflammation is a natural biological response triggered by the body's innate immune system to fight harmful insults such as infections and is needed to protect us from cancer. In normal physiology, inflammation is usually successfully resolved after a certain time when the stimulus is no longer there. However, if inflammation is not properly resolved, the immune cell infiltration and cytokine secretion are maintained long-term. This leads to harmful chronic inflammation, usually of lower intensity and longer duration than the physiological inflammation in response to damage, and is found in cancer and other pathological conditions such as autoimmune diseases, inflammatory conditions, or cardiovascular risk.[5] Interestingly, systemic inflammation, measured by CRP levels can be used to stratify patients according to cancer-related mortality risk.[6]

The major regulators of inflammation are cytokines, which are small secreted molecules involved in cell-to-cell communication. Chemokines are an important subfamily of these molecules, which mediate the migration and recruitment of leukocytes.[7] Cancer and stromal cells secrete multiple signaling molecules, including cytokines and chemokines, that promote the infiltration and regulation of the immune cells within the TME. In turn, recruited leukocytes and other stromal cells can produce a wide variety of pro-inflammatory cytokines, including interleukin-6 (IL-6) family cytokines, generating feedforward positive loops. These inflammatory responses activate transcription factors that are broadly implicated in cancer development and progression, including the signal transducer and activator of transcription 3 (STAT3), the hypoxia-inducible factor 1 alpha (HIF1α), and the nuclear factor-κB (NF-kB), whose activity controls the further production of inflammatory mediators.[8–10] Therefore, chronic inflammation plays an

essential role in the plasticity of TME and builds up a pro-tumorigenic microenvironment that favors tumorigenesis, immunosuppression, and cancer progression.[3]

IL-6 and related cytokines are considered the critical lynchpins between inflammation and cancer.[11] The IL-6 family encompasses multiple members: IL-6, oncostatin M (OSM), leukemia inhibitory factor (LIF), IL-11, IL-27, IL-31, ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CTF1), and cardiotrophin-like cytokine factor 1 (CLCF1). IL-6 family cytokines signal through heterodimeric receptors that share the glycoprotein 130 (gp130) subunit for signal transduction except for the IL-31 receptor, which binds a similar gp130-like receptor.[12] After ligand binding, the ligand-specific subunits dimerize with gp130 and phosphorylate tyrosine kinases such as Janus kinases (JAK) 1, 2, and Tyk2. This triggers the activation of multiple intracellular pathways including phosphoinositide 3-kinases, mitogen-activated protein kinase (MAPK), and STAT factors. STAT3 is the main mediator underlying the tumor-promoting effects of these cytokines, as its activation favors the transcription of genes related to proliferation, survival, recruitment, differentiation, and transformation.[13]

Notably, most IL-6 family cytokines have been linked to poor prognosis in patients with cancer due to their cancer-promoting effects in a wide range of tumors.[11] In particular, IL-6, OSM, LIF, and IL-11 (although much less studied) exert important pro-metastatic, pro-angiogenic, and immunosuppressive roles.[14–19] At the same time, there are still controversies about the function of other family members, which have been poorly evaluated in the cancer context. For example, epithelial–mesenchymal transition (EMT) is a key process during cancer progression, metastasis, and therapy resistance, and IL-6 cytokines (mainly IL-6, OSM, IL-11, and LIF) have been shown to promote EMT through the activation of transcription factors such as STAT3 and Snail. However, some anti-EMT functions have also been described for this cytokine family, mainly for IL-27 via STAT1 activation.[20]

In a non-tumor context, an inflammatory response is generated after an injury to repair the harm caused. This acute response is strongly regulated by extensive negative feedback mechanisms designed to decrease inflammation and prevent tissue damage once the injury is resolved. One of these mechanisms is the induction of the inhibitory immune checkpoints, such as programmed cell death receptor 1 (PD-1) and its ligand programmed cell death protein ligand 1 (PD-L1), lymphocyte-activation gene 3 (LAG3), cytotoxic T lymphocyte-associated protein-4 (CTLA-4), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), B and T lymphocyte attenuator (BTLA), and T cell immunoglobulin and ITIM domain (TIGIT). They are surface proteins found on T cells that bind to partner proteins in other cells, including cancer cells, and send an inhibitory signal to T cells. Importantly, tumors upregulate the activity and expression of these inhibitory immune receptors and ligands, resulting in T cell exhaustion and favoring tumor immune tolerance.[21] In this regard, the therapeutic strategy of blocking the activation of immune checkpoints with specific antibodies is known as immune checkpoint blockade (ICB) and has been translated to the clinic to treat many cancer types. ICB discovery is considered one of the greatest advances in medical oncology history and, currently, blocking antibodies targeting PD-1, PD-L1, and CTLA-4 are approved for treating melanoma, renal, breast, and lung carcinomas, among others.[22] Although it has brought many benefits for patients with cancer, many limitations remain to overcome, of which associated toxicity and the large number of refractory patients remain the most challenging.[22] In the last years, several mechanisms of resistance to ICB have been described, and they have been elegantly reviewed by Kalbasi and Ribas.[23] This knowledge led to the design of different combination therapies based on the hypothetical synergistic effects of interrupting different immune escape pathways, and those are currently being tested in clinical trials.

One of the most interesting approaches to overcoming resistance to ICB is modulating the immune TME by targeting cytokine signaling. In this review, we discuss how the IL-6 cytokine family can modulate the immune TME (figure 1) and how combining ICB and the blockade of IL-6-related cytokine signaling can potentially improve cancer immunotherapy (figure 2). We focus mainly on IL-6, LIF, and OSM, as their role in cancer is well-established and extensively characterized. Furthermore, we summarize the potential clinical use of cytokine-blocking antibodies and other cytokine-targeting drugs in the context of immunotherapy.

INTERLEUKIN-6

IL-6 signaling and functions in health and disease

IL-6 is a multifaceted cytokine that, depending on the context, is able to stimulate inflammatory and anti-inflammatory events. Besides, this cytokine has a broad action on a wide variety of immune and non-immune cells[24] (figure 3). IL-6 was discovered in 1986 as a B cell immunoglobulin-inducing factor, and nowadays, multiple functions of this cytokine have been identified. IL-6 is involved in the generation of acute phase proteins, immune responses against pathogens, inflammation, hematopoiesis, apoptosis, cell differentiation, bone homeostasis, angiogenesis, and metabolism. In addition to the role of IL-6 in the regulation of whole-body metabolism, changes in metabolism, such as obesity, can drive inflammation, increase IL-6 levels and promote immune tolerance, pointing to a reciprocal and complex regulation between inflammation and metabolism.[25] During inflammation and infection, IL-6 is commonly induced by IL-1 and tumor necrosis factor-alpha (TNF-α), but its expression can also be promoted through pathogenic stimulation of Toll-like receptors, prostaglandins, stress responses, adipokines, and other cytokines.[26] Three different mechanisms of IL-6 signaling have been

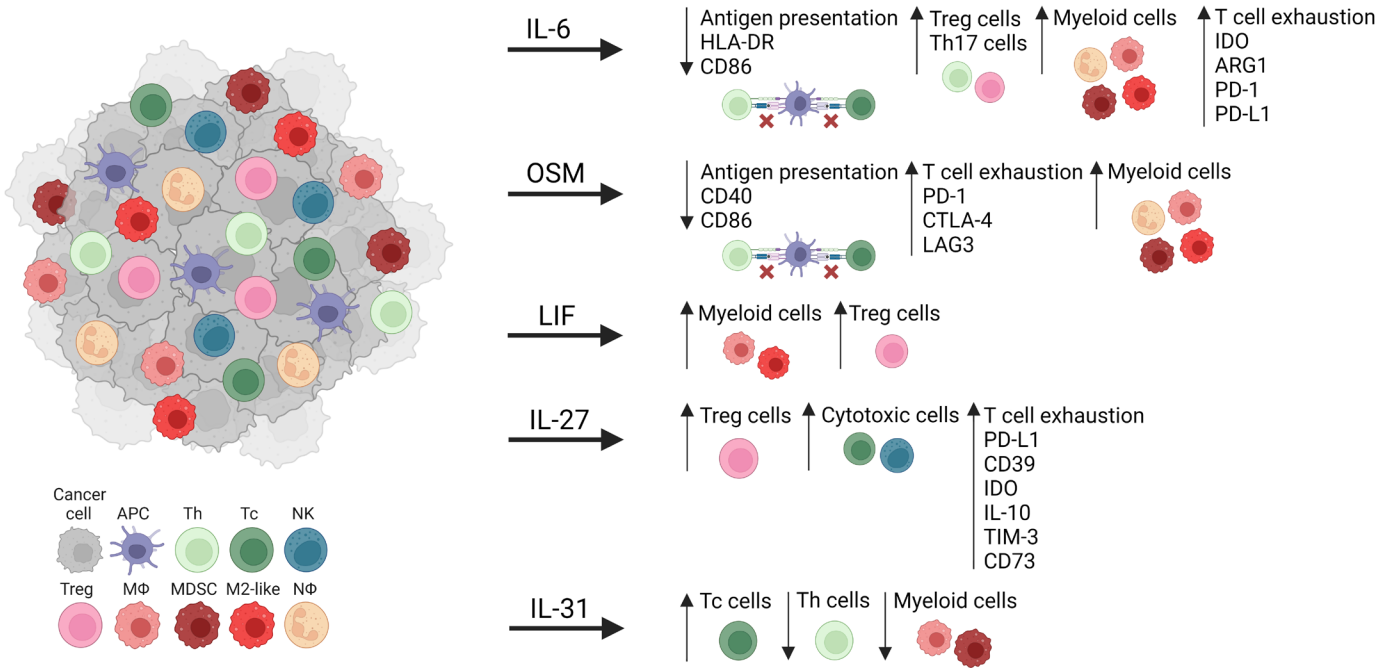

Figure 1 Modulation of the immune tumor microenvironment (TME) by IL-6 family cytokines. Graphical representation of the reported effects of the different IL-6 family cytokines on the different cell types within the TME. To our knowledge, there is no information about the cell types that are not depicted for each cytokine. APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte-associated protein-4; HLA, human leukocyte antigen; IL, interleukin; LAG3, lymphocyte-activation gene 3; LIF, leukemia inhibitory factor; M2-like, M2-like macrophage; MDSC, myeloid-derived suppressor cell; MΦ, macrophage; NΦ, neutrophil; NK, natural killer; OSM, oncostatin M; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death protein ligand 1; Tc, T cytotoxic; Th, T helper; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; Treg, T regulatory.

described: the classical activation pathway, the IL-6 trans-signaling, and the IL-6 cluster signaling, also known as trans-presentation signaling.[27] The classical activation pathway involves IL-6-binding to membrane-bound IL-6 receptor (mIL-6R) to induce a signal-transducing homodimer of the glycoprotein 130 (gp130) receptor. Additionally, there are soluble forms of the IL-6 receptor (sIL-6R), consisting of the extracellular portion of the IL-6R and generated either by limited proteolysis or alternative splicing.[28] These sIL-6R forms complex with IL-6 to activate membrane-bound gp130, in a process known as IL-6 trans-signaling.[29] Finally, cluster or trans-presentation signaling involves the activation of gp130 subunits through their binding to IL-6-mIL-6R complexes present in neighboring transmitter cells.[30] Interestingly, the expression of mIL-6R has been found mainly in hepatocytes and some subpopulations of leukocytes, and its activation is associated with acute inflammatory, homeostatic and regenerative effects. On the other hand, the sIL-6R trans-signaling activation is connected to IL-6 pro-inflammatory functions and pathological states.[31] Trans-presentation signaling is involved in the priming of pathogenic T helper 17 (Th17) cells.

IL-6 signaling is dynamic and highly regulated because its over-activation can result in several inflammatory pathologies, autoimmune diseases, and cancer development.[31] In the cancer context, activation of IL-6 signaling is associated with tumor growth, angiogenesis, metastasis, reprogramming of cancer cell metabolism, resistance to therapies, cachexia, and immune tolerance.[19 32 33] Moreover, high levels of IL-6 are found in patients with multiple myeloma, melanoma, breast, ovarian, cervical, prostate, pancreatic and lung cancer, among others, where they are associated with poor prognosis and therapy resistance.[34]

Modulation of the TME by IL-6 and implications in immunotherapy

IL-6 is the most studied member of the family and large and solid evidence supports that IL-6 is a promising candidate for therapeutic targeting in cancer, alone or in combination with other cancer therapies. The primary source of IL-6 in cancer is the tumor cell compartment together with fibroblasts, tumor-associated macrophages (TAMs), CD4+ T cells, and myeloid-derived suppressor cells (MDSCs)[19] (figure 3). IL-6 inherently affects tumor cells and the TME to support cancer progression at all stages from tumorigenesis to metastasis.

During early stages of carcinogenesis, IL-1 triggers inflammation and induces the release of cytokines, including IL-6 that further perpetuate the inflammatory state.[32] In addition, IL-6 promotes tumor cell survival and inhibits apoptosis by STAT3-dependent activation of genes such as BCL2, BCL-XL, MCL1, and survivin, which are critical for tumor development.[35–37] IL-6 signaling also drives tumor progression by promoting tumor invasiveness, cell migration and

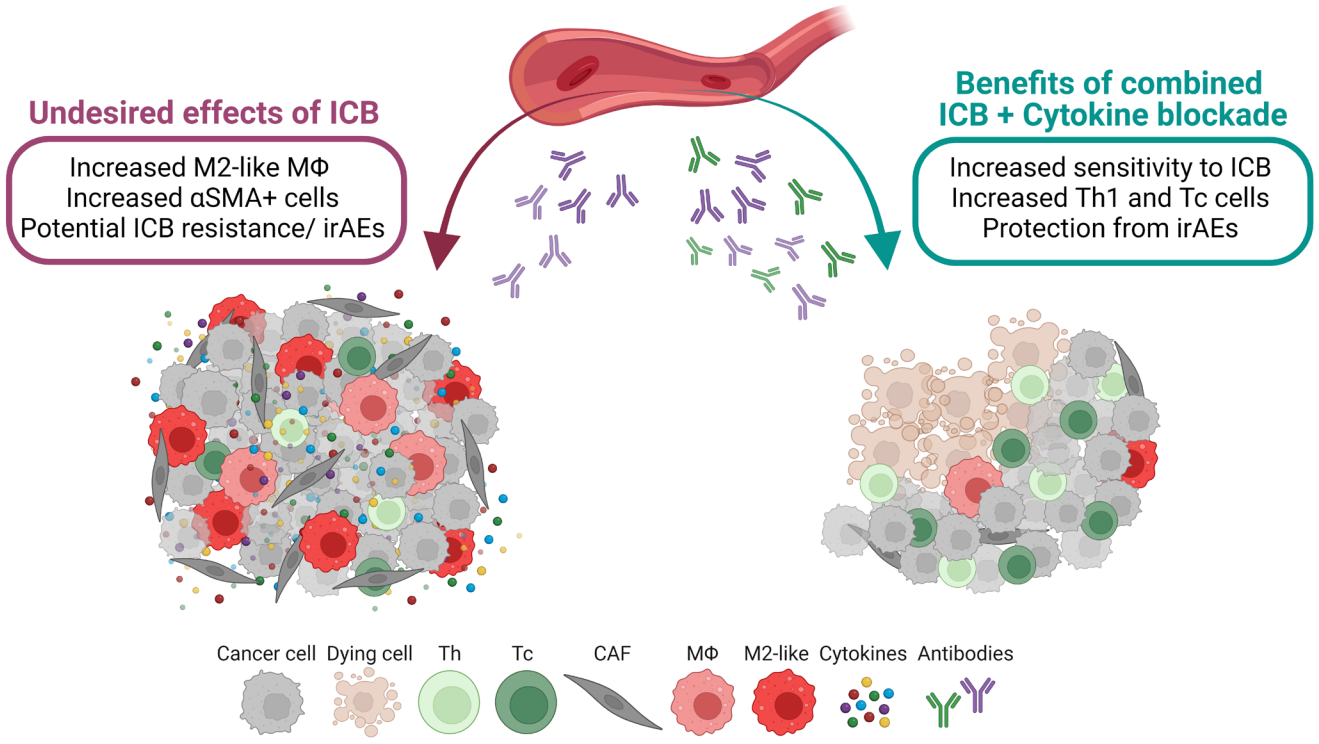

Figure 2 Benefits of combining immune checkpoint blockade (ICB) and cytokine blockade therapy. IL-6 family cytokines mediate resistance to ICB and immune-related adverse events (irAEs). Blockade of cytokines from the IL-6 family is a promising therapeutic approach to improve the efficacy of ICB. αSMA, alpha smooth muscle actin; CAF, cancer-associated fibroblast (αSMA+); IL-6, interleukin-6; MΦ, macrophage; M2-like, M2-like macrophage; Th, T helper; Tc, T cytotoxic.

metastasis via activation of matrix metalloproteinases and by mediating angiogenesis via the production of VEGF.[38 39] Furthermore, reprogramming cancer cell metabolism and induction of hypoxia signaling by IL-6 also contribute to tumor progression and promote immune tolerance.[33]

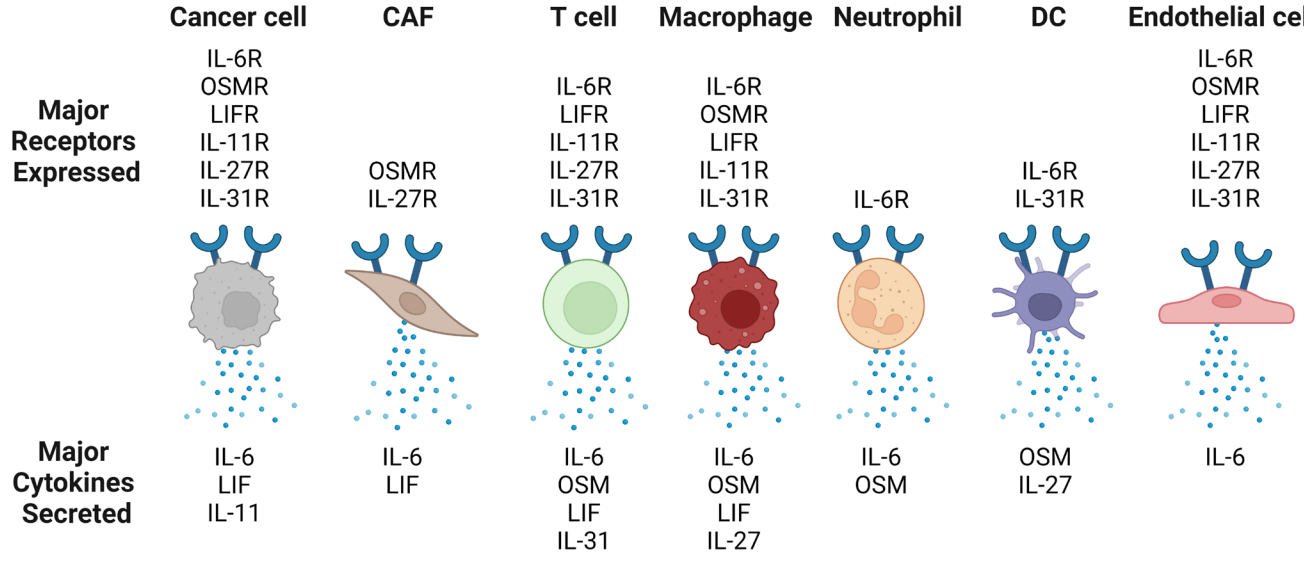

Figure 3 Secretion of IL-6 family cytokines and expression of related receptors by the different cell types within the tumor microenvironment (TME). CAF, cancer-associated fibroblast; DC, dendritic cell; IL, interleukin; LIF, leukemia inhibitory factor; OSM, oncostatin M.

Finally, IL-6 also exerts an essential role in promoting metastasis through different mechanisms. For example, IL-6 hijacks the hematopoietic stem and progenitor cell differentiation program towards pro-metastatic monocyte-dendritic progenitors, that differentiate into immunosuppressive macrophages and contribute to priming the pre-metastatic niche.[40] IL-6 is particularly important in bone metastasis due to its critical roles in bone metabolism. IL-6 favors bone metastasis by promoting osteolysis and cancer cell homing in the bone marrow niche.[41 42]

Besides, IL-6 indirectly modulates other processes within the intricate TME to support tumor development, as it sustains a pro-tumorigenic milieu that facilitates tumor evasion of immune surveillance.[43] In fact, IL-6 contributes to innate and adaptive immunity dysfunction and is a potent orchestrator of tumor-promoting inflammation, mainly through STAT3 activation[32] (figure 1). IL-6 promotes the recruitment and differentiation of immunosuppressive myeloid cells such as MDSCs and TAMs.[44–46] Regarding its role in adaptive immunity, IL-6 inhibits antigen presentation by reducing human leukocyte antigen (HLA)-DR and CD86 expression, promoting arginase activity and inducing immunosuppressive genes such as Arg1 and IDO. These effects lead to impaired activation of antigen-specific CD4+ T cells and to activation of pro-tumorigenic T-regulatory (Treg)/Th17 cell responses, driving immune tolerance.[46–49]

IL-6 also upregulates the expression of immune checkpoints in different cancer models,[50 51] suggesting that blockade of IL-6 may downregulate PD-1 and PD-L1 and result in decreased response to ICB. However, the combination of IL-6 targeting agents with ICB has been very successful in preclinical studies, probably due to the direct effects of IL-6 in cancer cells and its aforementioned immunosuppressive effects in other immune cell populations. In this sense, dual inhibition of IL-6 and CTLA-4 has been shown to enhance survival and reduce tumor progression in lung and pancreatic cancer models.[52 53] Similarly, the combination of IL-6 inhibition and PD-1/PD-L1 blockade exerts synergistic effects in melanoma, glioblastoma, B-cell acute lymphoblastic leukemia, colon, breast, pancreatic, and hepatocellular carcinoma mouse models.[50 54–57] In those experimental models, IL-6 blockade modulated the tumor immunological characteristics by increasing T-cell infiltration, enhancing tumor-specific cytotoxic T lymphocyte (CTL) and Th1 responses, and reducing PD-L1 expression.[50 53–56] Importantly, IL-6 has been considered a predictive marker of ICB response. Many studies demonstrated a correlation between circulating IL-6 levels, decreased survival, and clinical response to ICB.[55 56 58 59] Plasma and serum IL-6 levels predicted response to the PD-1 pathway inhibitors atezolizumab and nivolumab in patients suffering melanoma, advanced kidney, breast, and bladder cancers, and metastatic non-small-cell lung carcinoma (NSCLC),[55 56 58] and to CTLA-4 blockade in patients with small cell lung cancer (SCLC).[59]

In addition, IL-6 has also been implicated in aggravating the immune-related adverse events (irAEs) associated to ICB.[60–62] IrAEs are common in immunotherapy, and mitigating these toxic effects has become a major challenge.[22] Hailemichael *et al.* have recently described that IL-6R inhibition alleviates ICB autoimmunity by reducing Th17 differentiation, secretion of pro-inflammatory cytokines, and neutrophil chemotactic proteins in damaged tissues of patients and mice receiving ICB. Besides, the abrogation of the IL-6 cytokine pathway increased Th1 and CD8+ T effector cells in the tumor, boosting antitumor immunity.[63] In this sense, observational clinical data support that combining the anti-IL-6R antibody tocilizumab with ICBs may effectively manage irAEs and prevent autoimmune disease flare-ups.[61] In fact, tocilizumab is approved for treating severe chimeric antigen receptor T (CAR-T)-cell-induced cytokine release syndrome.[64]

ONCOSTATIN M

OSM signaling and functions in health and disease

OSM was first described as a growth regulator that inhibited the proliferation of different tumor cell lines but not normal human fibroblasts, hence its name.[65] However, the extreme complexity of its role in physiology and disease has become evident. This evidence is still increasing as many studies prove it plays multiple functions in hematopoiesis, mesenchymal stem cell differentiation, liver regeneration, heart remodeling, nociception, inflammation, wound healing, fibrosis, and metabolism. Thus, OSM is considered a pleiotropic cytokine, and its role in health and disease has been extensively reviewed.[66–68]

OSM signaling shows unique characteristics. While most IL-6 family cytokine–gp130 interactions are of low affinity in the absence of binding to their specific α-receptor (eg, IL-6R, LIFR), OSM binds first to gp130 as a low-affinity α-receptor and then to its specific receptor β OSMR.[68] In addition, OSM is the only cytokine in the family that can engage two β-receptors in humans (ie, OSMR and LIFR), being the gp130/OSMR complex the main mediator of most OSM effects.[17 18 69 70] Interestingly, the OSMR β-receptor can bind to the specific IL-31 α-receptor to form the IL-31 receptor complex.[68] Despite the complexity of OSM signaling and the functional redundancy of some IL-6 family cytokines, OSM-gp130/OSMRβ complex has been shown to activate specific signaling pathways providing evidence that OSM serves unique physiological and pathological functions.[68] Unlike gp130, OSMR efficiently induces tyrosine phosphorylation of the Shc isoforms p52 and p66 and their association with Grb2, allowing OSM to drive more potent ERK/MAPK pathway activation than IL-6 or LIF.[71] Moreover, OSMR can also induce STAT5a, STAT5b, Akt, c-Jun N-terminal kinase (JNK), p38, and PKCd activation in a context-dependent manner.[72–75]

The main OSM producers are activated monocytes, macrophages, neutrophils, T lymphocytes, and dendritic cells (figure 3). Its specific receptor OSMR, in contrast,

is widely expressed by most of the non-hematopoietic mesenchymal cells (eg, endothelial cells, fibroblasts, smooth muscle cells, adipocytes, osteoblasts) as well as hepatocytes, glial cells, mesothelial and epithelial cells from numerous organs.[68]

Although it shows antiproliferative effects in some cancer cells in vitro,[65] it is now well accepted that OSM promotes pro-tumorigenic features and correlates with poor prognosis in multiple cancer types such as glioblastoma, breast, gastric, pancreatic, and cervical cancers.[17 18 76–78] In cancer cells, OSM promotes malignancy through the induction of processes such as EMT, cancer stem cell-like properties, migration, invasion and both tumorigenic and metastatic capacity.[20 70 76 77 79–84] Moreover, recent studies have demonstrated that OSM is also a major activating factor of the stroma as it can promote angiogenesis, fibroblast activation, fibrosis, and ECM remodeling, representing a key molecule in the immune-stroma crosstalk in health and disease.[17 18 67 85 86]

Modulation of the TME by OSM and implications in immunotherapy

In addition to its roles in cancer and stromal cells, our group and others have shown that OSM is also an important regulator of the immune TME[17 18] (figure 1). We recently described that myeloid-derived OSM promotes chemokine secretion and recruitment of macrophages and Ly6G+ cells in breast cancer.[17] In line with these results, Lee *et al*. elegantly showed that OSM supports the generation of a pancreatic cancer immunosuppressive microenvironment.[18] In this work, the TME of Osm-/- animals shifted toward more immunogenic T and myeloid cell phenotypes, where infiltrated T cells showed reduced T cell exhaustion features and inhibitory surface markers like CTLA-4, LAG3, and PD-1. Additionally, monocyte differentiation into an immunosuppressive TAM phenotype was impaired. This switch was accompanied by higher expression levels of co-stimulatory molecules such as CD40 and CD86 in antigen-presenting cells (APCs) and a marked reduction of cytokines, including GM-CSF, IL-6, CXCL1, and TNF-α. In silico analyses of glioblastomas showed that OSM expression is associated with stromal and immune cell infiltration in the TME and with the expression of immune checkpoint regulators.[84]

The information regarding the implications of OSM signaling in cancer immunotherapy is still scarce. However, it is not unreasonable to hypothesize that combinatorial OSM inhibition could benefit different immunotherapeutic approaches. Multiple studies showed that targeting macrophages and granulocytes (leading OSM producers) relieves immunosuppression, increases T cell infiltration, and sensitizes tumors to ICB.[87 88] Moreover, OSM has been shown to indirectly induce the accumulation of M2-like macrophages in the TME.[89 90] Likewise, OSM prompts cancer-associated fibroblast (CAF) activation by promoting FAP expression, CAF proliferation, and CXCL12 secretion in breast and pancreatic cancers[17 18] and it has been demonstrated that targeting CXCL12 from FAP-expressing CAFs synergizes with anti-PD-L1 immunotherapy in pancreatic cancer.[91] These preclinical studies support that OSM inhibition may exert potent anticancer effects through different mechanisms that can cooperate, including inhibition of migration, angiogenesis and metastasis, ECM remodeling and promotion of antitumor immunity.

LEUKEMIA INHIBITORY FACTOR

LIF signaling and functions in health and disease

Like OSM, LIF was described as an antiproliferative and pro-differentiation cytokine in M1 murine myeloid leukemia cells.[92] Interestingly, both OSM and LIF share high structural and functional homology and are thought to result from duplication of a common ancestral gene.[93] Both cytokines act on a wide range of cells and elicit diverse overlapping biological responses that can be explained by their shared gp130 subunit and the ability of OSM to bind both OSMR and LIFR. LIF is produced by nearly every healthy tissue and cell type, and the same ubiquitous expression applies to its specific receptor LIFR.[94 95] In contrast, as mentioned in the previous section, OSM expression is restricted to immune cells and OSMR is expressed mainly by mesenchymal and epithelial cells.[17 68] This differential expression could explain the non-redundant effects of LIF during blastocyst implantation, placental formation, development of the nervous system and maintenance of self-renewal and totipotency of both embryonic and induced pluripotent stem cells.[96]

Within cancers, LIF mRNA is expressed by epithelial carcinoma cells,[97] surrounding stromal cells, and immune cells like T-cells, macrophages, and monocytes[98] (figure 3), and the expression of both the ligand and the receptor is often dysregulated in tumors compared with healthy tissue.[14] The role of the LIF/LIFR pathway in cancer is controversial as LIF can exert both pro-cancer and anticancer effects in different tumor types.[14 96] For instance, LIF increases the self-renewal capacity of glioma-initiating cells and prevents their differentiation by activating the JAK-STAT pathway.[15] The activation of the mTORC1/p70S6K pathway is critical for the LIF-dependent tumor-promoting effects and radioresistance in nasopharyngeal carcinoma.[99] In pancreatic cancer, oncogenic KRAS drives LIF expression[100] and pancreatic-stellate-cell-secreted LIF activates pro-tumorigenic features on cancer cells and promotes inflammatory CAF formation.[101 102] On the other hand, in the context of breast cancer, LIFR suppresses metastasis by induction of the Hippo-YAP pathway[103] and contributes to maintaining disseminated cells in a dormant state inside the bone marrow, preventing them from colonizing it.[104] LIF has been involved in many other cancer-related processes, such as tumor growth, proliferation, apoptosis, migration, invasion, metastasis, and therapeutic resistance.[14] In addition, the effects of LIF in the stromal compartment have been confirmed in different cancer models, where

LIF drives the conversion of fibroblasts into pro-invasive CAFs.[105]

Modulation of the TME by LIF and implications in immunotherapy

Like other family members, LIF also has immunosuppressive functions (figure 1). It promotes, together with IL-6, M2 macrophage and TAM polarization and inhibits T cell function.[45 106 107] It also stimulates the expansion and activation of polymorphonuclear MDSCs in prostate cancer.[108] In line with these results, Pascual-García *et al.* observed that LIF is associated with the presence of pro-tumorigenic TAMs in different cancer types, including glioblastoma, prostate, thyroid, and ovarian cancer. LIF blockade in tumors expressing high levels of this cytokine triggered CD8+ T cell tumor infiltration by releasing the epigenetic silencing of CXCL9. The regulation of CD8+ cell infiltration by LIF has direct implications for ICB efficacy and blockade of LIF with neutralizing antibodies synergized with anti-PD-1 blockade in glioblastoma models.[109] Importantly, an unbiased proteomic analysis recently identified that high baseline plasma levels of LIF were associated with poor clinical outcomes in patients with cancer treated with ICB.[110] The authors also showed that LIF levels were inversely correlated with the presence of tertiary lymphoid structures in the TME. However, low baseline serum levels of LIF have been associated with hyper-progressive metastatic gastrointestinal cancer among patients receiving ICB,[111] and the role of LIF as a predictive biomarker for ICB needs further investigation.

In summary, there is solid preclinical evidence on the immunosuppressive role of LIF. In preclinical syngeneic colon cancer mouse models, the anti-LIF blocking antibody MSC-1 reprogrammed macrophages to acquire anti-tumor and pro-inflammatory functions and enhanced the efficacy of anti-PD-1 therapies.[107] Interestingly, the role of LIF could also be studied in the context of anti-cancer vaccines, as a recent report showed that immunization against LIF and LIFR prevented tumor formation in BALB/c mice.[112]

OTHER MEMBERS OF THE IL-6 CYTOKINE FAMILY

IL-27, structurally related to both IL-6 and IL-12 families, could also be considered a potential target to alter the tumor immune response.[113 114] However, its dual role in cancer immunology and its pleiotropic functions, reviewed in Fabbi *et al.*,[113 113] should be considered in the design of clinical trials and could limit its applications in cancer immunotherapy. IL-27 induces natural killer (NK) and T cell cytotoxicity, but it can also enhance Treg activity and upregulate immunosuppressive molecules, including PD-L1, CD39, IDO, IL-10, TIM-3, and CD73[115–119] (figure 1). IL-27 was identified as part of an eight-gene signature capable of predicting survival, expression of immune checkpoints, and immune cell infiltration in breast cancer.[120] IL-27 exerts immunosuppressive functions and is usually secreted by APCs and MHC-expressing CAFs[121] (figure 3). Considering the available evidence, the strategy of blocking IL-27-induced immunoregulatory effects in combination with anti-PD-1/PD-L1 antibodies or IDO inhibitors could be a better choice than blocking IL-27 alone.[113]

IL-31, another family member, also seems to have a dual role in cancer. On the one hand, it promotes anti-tumor immunity[122] and inhibits tumor growth.[123] In this sense, IL-31 increased cytotoxic T-cell infiltration in breast tumors and negatively regulated immunosuppressive cell populations[122] (figure 1). On the other hand, IL-31 increased the proliferation of human follicular lymphoma cells, and IL-31 and IL-31R levels in lymph nodes were associated with tumor grade.[124] In the context of ICB, IL-31 was proposed as a therapeutic target to alleviate irAEs, as it was increased in the skin of patients with pruritic cancer who had been treated with PD-1 inhibitors.[125]

Recombinant IL-11 is approved to prevent and treat thrombocytopenia in patients with cancer receiving chemotherapy.[126] However, due to its effect on cell tumorigenicity and metastasis, its inhibition has been proposed as a potential therapeutic strategy for some cancer types.[127 128] Together with IL-6, IL-11 orchestrates inflammation and innate immune responses through activation of STAT3.[32 129 130]

Finally, the expression of CLCF1, a member of the family poorly studied in the context of cancer, was associated with poor prognosis and reduced response to anti-PD-1/PD-L1 antibodies in glioma.[131]

THERAPEUTIC STRATEGIES TO BLOCK IL-6 CYTOKINE FAMILY SIGNALING

Potential therapeutic strategies aimed at blocking IL-6 cytokines fall mainly into two categories: monoclonal antibodies (mAbs) targeting cytokines or their receptors, and small molecules (eg, antagonists or inhibitors) that interfere either with the ligand-receptor signaling complexes or the downstream JAK-STAT signaling pathways.[19] Here, we describe the different approaches to therapeutically block the signaling of IL-6 cytokines, emphasizing those studied in solid tumors.

Cytokine and cytokine-receptors blockade

Anti-IL-6 therapies are the most studied in cancer due to their widespread clinical use in inflammatory and autoimmune diseases.[66] The anti-IL-6R mAbs tocilizumab, sarilumab, and satralizumab, and the anti-IL-6 antibody siltuximab are approved for the treatment of inflammatory conditions such as rheumatoid arthritis and Castleman disease, and CAR-T-associated cytokine release syndrome.[64 132] Furthermore, other IL-6-IL-6R targeting antibodies and fusion proteins such as sgp130Fc, designed to selectively inhibit IL-6 trans-signaling by targeting IL-6–sIL-6R complexes are being evaluated in clinical trials.[19 133] In general, the main adverse effects of anti-IL-6/IL-6R antibodies are related to bacterial infections,

possibly due to the importance of IL-6 in coordinating innate and adaptive immune responses and in the activation of acute phase response.[66] Inhibition of IL-6 trans-signaling may have significant advantages since it does not affect the IL-6 classical signaling pathway, and, therefore, the immune response against infections is not affected. In addition, the main deleterious pro-inflammatory effects of IL-6 are mediated through trans-signaling.[27]

Drugs targeting other cytokines of the family have not been approved yet, but humanized antibodies against LIF and IL-27 are currently under clinical investigation for treating patients with cancer and anti-OSM and OSMR mAbs for inflammatory diseases.[66] The anti-LIF (MSC-1) and the anti-IL-27 (SRF388) mAbs proved to be well tolerated in patients with cancer[134 135] and are currently in phase 2 clinical trials for the treatment of advanced solid tumors. Although they have not been tested in the cancer setting, OSM (GSK2330811 and GSK315234) and OSMR (vixarelimab) blocking antibodies have proven to be well tolerated[136 137] and are now in Phase 2 clinical trials for the treatment of different inflammatory diseases. GSK2330811 and GSK315234 were discontinued due to lack of efficacy and safety problems.[138 139] The most important adverse effects were anemia and thrombocytopenia.[138] Although this toxicity was not acceptable for systemic sclerosis, a chronic condition requiring long treatments, it may be manageable for patients with advanced cancer.

Blocking cytokines or cytokine receptors can have different effects. In view of the existing data, targeting cytokine receptors can result in greater efficacy and decreased toxicity than targeting cytokines. For example, anti-IL-6 antibodies can substantially increase systemic IL-6 levels by trapping IL-6 in circulation.[24] This increase can induce hypercalcemia, fever, and fatigue due to high IL-6 blood concentrations. In addition, mAbs against cytokine receptors can block the effect of various cytokines. Blocking IL-6R will prevent its activation by its specific ligand and other ligands, such as IL-30 and CNTF. Something similar may happen with LIFR, as part of the effects of LIFR inhibitors have been linked to joint blocking of LIF, OSM, CTF1, and CNTF.[140]

JAK-STAT signaling inhibition

Several JAK competitive inhibitors (the JAK1/2-selective inhibitors ruxolitinib and barcitinib, and the JAK1/3 inhibitor tofacitinib) are approved for the treatment of myeloproliferative disorders, rheumatoid arthritis, and COVID-19.[19 141] Although they have generally been well tolerated, they have showed limited efficacy in clinical trials for solid tumors.[66] A wide array of adverse effects has been reported in patients treated with JAK inhibitors, which have been attributed to their specificity to different JAKs. Although these effects include bacterial, mycobacterial, fungal, and viral infections, anemia, thrombocytopenia, neutropenia, gastrointestinal intolerance, transaminitis, and neurotoxicity, they have not hindered the approval of JAK inhibitors in the clinic.[142]

Despite the critical role of STAT3 in cancer and tumor-promoting inflammation, the clinical development of its inhibitors has been difficult because STAT3 is an intracellular transcription factor.[9] However, a few STAT3 inhibitors are currently being tested in clinical trials including patients with cancer, where they have showed to be well tolerated.[143 144] The STAT3 inhibitors under clinical development are mainly antisense oligonucleotides (such as AZD9150) and non-peptide STAT3–SH2 domain antagonists that prevent STAT3 dimerization.

Inhibiting IL-6 cytokine signaling using JAK and STAT3 inhibitors could be more effective in blocking cancer-promoting inflammation than blocking upstream with cytokine or cytokine receptor blocking antibodies. However, this strategy may impair not only IL-6 family signaling but also many other cytokines, interferons, and hormones, and it may entail more significant adverse effects.

Combination therapies including IL-6 cytokine family blockade

Blocking immunosuppression elicited by cancer-promoting inflammation is essential to effectively treat cancer and improve the efficacy of current treatments, including immunotherapy, which shows limited efficacy in some solid tumors. Targeting chronic inflammation is difficult due to its high complexity, its regulation by multiple interactive pathways, and numerous compensatory mechanisms. These drawbacks may explain why cytokine-targeting drugs have been ineffective in blocking tumor progression in monotherapy. However, the strong preclinical evidence described in previous sections supports that blocking IL-6 family cytokine signaling in combination with ICB may be an attractive therapeutic strategy for patients with cancer. Drugs targeting the IL-6 cytokine family may boost ICB efficacy and reduce irAEs (figure 2). Currently, there are about 20 active Phase I and II clinical trials evaluating the efficacy and safety of the combination of anti-IL-6R, anti-IL-6, anti-LIF, and anti-IL-27 antibodies with ICB in patients with solid tumors including melanoma, NSCLC, and urothelial and pancreatic carcinomas (table 1). The anti-IL-6R antibody tocilizumab is the most commonly used cytokine-targeting drug in those trials, tested in combination with the anti-PD-1 and PD-L1 antibodies atezolizumab, nivolumab, or ipilimumab. Even though the information regarding the role of OSM signaling in improving the efficacy of immunotherapy is still very limited, the clinical development of these blocking antibodies will probably boost the research on this topic. STAT3 and JAK inhibitors are also being tested in clinical trials in combination with ICB in patients with advanced cancer.[145] Interestingly, the JAK inhibitor ruxolitinib alleviated immune-checkpoint inhibitor-associated myocarditis.[146]

Therapeutic blockade of IL-6 cytokines could also be combined with chemotherapy, as some cytokines such as IL-6, OSM, and LIF promote chemoresistance and inhibit the chemotherapy-induced anticancer immune

Table 1 Summary of existing clinical trials combining immunotherapy and blockade of IL-6 family cytokines

Clinical trial (NTC number)	Target	Conditions	Interventions	Phase
NCT05022927	IL-6R	HCC	ERY974, tocilizumab, atezolizumab, bevacizumab	1
NCT04940299	IL-6R	Advanced Melanoma, NSCLC, urothelial carcinoma, bladder cancer	Ipilimumab, nivolumab, tocilizumab	2
NCT04729959	IL-6R	Recurrent glioblastoma, diffuse astrocytoma	Atezolizumab, conventional surgery, radiation, tocilizumab	2
NCT04691817	IL-6R	NSCLC	Atezolizumab, tocilizumab	1–2
NCT04524871	IL-6R	Advanced liver cancers	Atezolizumab, bevacizumab, tiragolumab, tocilizumab, TPST-1120, RO7247669	1–2
NCT04258150	IL-6R	Pancreatic cancer	Nivolumab, ipilimumab, tocilizumab, radiation	2
NCT03999749	IL-6R	Melanoma	Ipilimumab, nivolumab, tocilizumab	2
NCT03869190	IL-6R	Urothelial carcinoma, bladder cancer	Atezolizumab, enfortumab vedotin, niraparib, Hu5F9-G4, tiragolumab, sacituzumab govitecan, tocilizumab, cisplatin, gemcitabine	1–2
NCT03866239	IL-6R	Colorectal cancer	Obinutuzumab, atezolizumab, cibisatamab, tocilizumab	1
NCT03821246	IL-6R	Prostate cancer	Atezolizumab, tocilizumab, etrumadenant	2
NCT03708224	IL-6R	Head and neck squamous cell carcinoma	Atezolizumab, tocilizumab, tiragolumab	2
NCT03424005	IL-6R	Triple negative breast cancer	Capecitabine, atezolizumab, ipatasertib, SGN-LIV1A, bevacizumab, gemcitabine+carboplatin or eribulin, selicrelumab, tocilizumab, nab-Paclitaxel, sacituzumab govitecan	1–2
NCT03337698	IL-6R	NSCLC	Atezolizumab, cobimetinib, RO6958688, docetaxel, CPI-444, pemetrexed, carboplatin, gemcitabine, linagliptin, tocilizumab, ipatasertib, bevacizumab, sacituzumab govitecan, radiation, evolocumab	1–2
NCT04191421	IL-6	Metastatic pancreatic adenocarcinoma	Siltuximab, spartalizumab	1–2
NCT05428007	IL-6R	Melanoma	Sarilumab, ipilimumab, nivolumab, relatlimab	2
NCT04999969	LIF	Locally advanced or metastatic solid tumors	AZD0171, durvalumab, gemcitabine, nab-paclitaxel	2
NCT05061550	LIF	NSCLC	AZD0171, durvalumab, oleclumab, monalizumab, MEDI5752, dato-DXd, pemetrexed, carboplatin, cisplatin, paclitaxel	2
NCT04374877	IL-27	Advanced ccRCC or HCC, or anti-PD(L)1 relapsed/refractory advanced NSCLC	SRF388, pembrolizumab	1
NCT05359861	IL-27	HCC	SRF388, atezolizumab, bevacizumab, placebo	2

ccRCC, clear cell renal cell carcinoma; HCC, hepatocellular carcinoma; IL-6, interleukin-6; LIF, leukemia inhibitory factor; NSCLC, non-small cell lung cancer; PD(L)1, programmed cell death protein ligand 1.

response.[57 101 147] Finally, blocking IL-6 cytokine, which significantly affects metabolic control, could have synergic roles with antimetabolic drugs such as LDH inhibitors or CD36 targeting agents.[148 149] Notably, high serum LDH is an important predictor of resistance to anti-PD-L1 immunotherapy.[150]

CONCLUSIONS AND FUTURE DIRECTIONS

IL-6-related cytokines are characterized by their multifunctionality, showing overlapping or redundant functions among members but also eliciting unique responses. They have direct effects on cancer cells. Up to date, most of them are considered tumor promoters, although antitumor responses have also been reported. Most of these family members seem to have the extraordinary ability to act on a wide variety of cells and ECM proteins within the TME. They can also modulate the intricate immune composition of the TME, promoting its activation, inhibition, or differentiation depending on the cell type. Among all the family members, IL-6 is the one showing the clearest and most drastic effects in the TME, being a master regulator of chronic

inflammation and a potent suppressor of immune antitumor responses.

The inhibition of these cytokines in preclinical murine models in combination with ICB has been shown to improve immunotherapy results. Therapeutic targeting of IL-6-related cytokines and their receptors could tip the balance to a more antitumor TME, and it is a valid and worth exploring alternative to block tumor-promoting inflammation (figure 2). A substantial number of clinical studies evaluating antibodies targeting IL-6 and IL-6-related cytokines in cancer are in combination with ICB (table 1). Moreover, recent studies have demonstrated the potential of these cytokines as predictive biomarkers of ICB therapy, supporting their relevant role in the therapeutic success of immunotherapies. Nevertheless, several issues regarding the combination of IL-6 cytokine family blockade with ICB therapy should be addressed. For example, the optimal schedule for the most effective combination should be evaluated. Based on the preclinical data supporting that IL-6 cytokines promote immunosuppression in the TME by inhibiting antigen presentation and promoting the activation of MDSCs, the combination of ICB and cytokine blockade could be more effective if cytokines were targeted first. Mathematical modeling can help to optimize time schedules and sequential combinations of drugs.[151] Ultimately, drug tolerance and toxicity of the co-inhibitory treatment must be considered.

In addition, a better understanding of the implications of this cytokine family in regulating the immune TME in the early and advanced setting for each tumor type is needed. In fact, the immune landscapes of primary tumors and metastases are very different.[152] Most clinical trials developed with IL-6 blocking therapies include patients with metastatic disease. This scenario may not be optimal as it may be too late to revert the immunosuppressive TME fostered by chronic inflammation. Actually, neutralizing inflammatory cytokines results in a sustained reduction of downstream cytokines in serum but induces disease stabilization only for short periods.[153] The ideal setting may be the neoadjuvant for non-advanced tumors and the first lines of treatment in the advanced stages.

Finally, predictive biomarkers are needed to incorporate IL-6 family-targeting agents into the repertoire of anticancer drugs. Comprehensive analyses of the immune landscape and cytokine profile of early and advanced tumors are key to designing rational therapeutic strategies and to choose suitable targets. In some cases, targeting various cytokines at a time may result in more potent antitumor effects than using cytokine-targeting drugs in monotherapy, as cytokines usually cooperate with other cytokines and chemokines and act in loops. For example, OSM has been shown to be a potent inducer of IL-6, LIF, and myeloid-recruiting chemokines.[17 18]

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